Job Ticket # 8417
05-Aug-2009 09:48:26
V501 / 2009-06028 / bgpk / US / a
Volume #1

GARDASIL Supplemental Biologics Licensing Application for Use in Boys and Men

Vaccines and Related Biological Products Advisory Committee (VRBPAC) Briefing Document

Research Laboratories

GARDASIL®

(Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine) -

Supplemental Biologics Licensing Application for Use in Boys and Men

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

Briefing Document

Presented to VRBPAC on

09-September-2009

TABLE OF CONTENTS

TABLE OF CONTENTS (CONT.)

LIST OF TABLES

LIST OF TABLES (CONT.)

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Experience
AIN	Anal Intraepithelial Neoplasia
AIS	Adenocarcinoma in situ
ANOVA	Analysis of Variance
BD	Bowen's Disease
BP	Bowenoid Papulosis
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment
cLIA	Competitive Luminex immunoassay
DNA	Deoxyribonucleic Acid
EGL	External Genital Lesion
EQ	Erythoplasia of Queyrat
FAS	Full Analysis set
GHN	Generally HPV Naive
GMT	Geometric Mean Titer
H&E	Hematoxylin and Eosin
HIV	Human Immunodeficiency Virus
HM	Heterosexual Men
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
MedDRA	Medical Dictionary for Regulatory Activities
mMU/mL	Milli Merck Units per Milliliter
MRL	Merck Research Laboratories
MSM	Men Having sex with men
NWAES	New Worldwide Adverse Experience System
OPSCC	Oropharyngeal Squamous Cell Carcinoma
Pap	Papanicolaou's Test
PCR	Polymerase Chain Reaction

Abbreviation	Definition
PIN	Penile/perianal/perineal intraepithelial neoplasia
PPE	Per-Protocol Efficacy
PSUR	Periodic Safety Update Report
RRP	Recurrent Respiratory Papillomatosis
SAE	Serious Adverse Experience
SAP	Statistical Analysis Plan
sBLA	Supplemental Biologics Licensing Application
SCC	Squamous Cell Carcinoma
SIL	Squamous Intraepithelial Lesion
SRC	Safety Review Committee
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infections
VaIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
VLP	Virus-Like Particles
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VRC	Vaccination Report Card
VSD	Vaccine Safety Datalink
VAERS	Vaccines Adverse Events Reporting System

1. Summary

In the United States, GARDASIL®[1] (human papillomavirus [Types 6, 11, 16, 18] recombinant vaccine) is indicated in women 9-26 years of age for prevention of human papillomavirus (HPV) 16/18-related cervical, vulvar and vaginal cancer, HPV 6/11-related genital warts, and HPV 6/11/16/18-related genital intraepithelial neoplasia. Safety data from clinical trials, postmarketing studies, and surveillance systems confirm the favorable safety profile of GARDASIL® in females and continue to support the benefit-risk profile of the vaccine.

HPV results in a substantial burden of disease in men as well as in women, and men play an important role in transmitting the virus to women. In adolescence and young adulthood, acquisition of HPV in males is high. Genital warts caused by HPV types 6 and 11 are one of the most common sexually transmitted diseases (STDs). Genital warts are associated with significant clinical and psychosocial burden in the patients, recur frequently despite different treatment modalities, and are infectious. In addition, HPV causes penile, anal, and oropharyngeal cancers in men, and HPV 16 and 18 are the most frequent types detected in these cancers. Unlike in women, there are no routine screening methods to identify HPV infection or precancerous lesions, and prevent progression of disease in men. To address this unmet medical need, clinical trials among boys and men have been an integral part of the comprehensive clinical development program of GARDASIL®.

Three studies (Protocols 016, 018 and 020) were conducted among 5402 boys and men 9-26 years of age in a diverse population from 6 continents and 23 countries. This age range covers the period before sexual debut through the period of peak risk for HPV infection and diseases. GARDASIL® is a prophylactic vaccine that provides greatest benefit if administered prior to exposure to HPV. Thus, preadolescents and young adolescents are the ideal age group to target for routine immunization. However, efficacy studies among sexually-naïve adolescents are not feasible. Therefore, in an approach similar to what was done in female studies, efficacy against HPV-related diseases was evaluated in sexually-active men 16-26 years of age and efficacy was bridged from this cohort to 9 to 15 year-old HPV-naïve boys by demonstrating non-inferiority of immunogenicity in this younger age group compared with the age group in whom vaccine efficacy was studied.

Protocols 016 and 018 evaluated immunogenicity and safety of GARDASIL® in preadolescents and adolescents, which included 1347 boys 9-15 years of age. These two studies provided the safety data from this age group and the basis of immunobridging between preadolescents/adolescents and adults.

Vaccine efficacy in males was evaluated in Protocol 020, a randomized, double-blind, placebo-controlled trial. A total of 4055 men were enrolled and received at least one dose of GARDASIL® or placebo to GARDASIL®. Of these, 3457 were heterosexual men (HM) aged 16 to 23 years and 598 were men having sex with men (MSM) aged 16 to 26 years. This study also provided safety and immunogenicity data.

[1] GARDASIL is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

The primary efficacy objective of Protocol 020 was met by demonstrating 90.4% (95% CI: 69.2, 98.1) efficacy against the predefined endpoint of HPV 6/11/16/18-related external genital lesions (EGLs), including external genital warts and penile/perianal/perineal intraepithelial neoplasia (PIN) of any grade in men 16-26 years of age. Of 34 cases of EGL, 31 were genital warts and all were positive for HPV 6 and/or 11. Protocol 020 demonstrated that GARDASIL® was 89.3% (95% CI: 65.5, 97.9) efficacious in preventing HPV 6/11-related external genital warts. GARDASIL® was also highly efficacious [85.6% (97.5% CI: 73.4, 92.9)] in preventing HPV 6/11/16/18-related persistent infection. Efficacy against persistent infection was similarly high for each of the vaccine HPV types, including carcinogenic types HPV 16 and 18. Efficacy was high in all populations examined, regardless of ethnicity, geographic region, smoking or circumcision status at baseline, and through a median of 2.9 years follow-up period post-dose 1. Results of efficacy analyses among all subjects (regardless of HPV status at onset of vaccination) also support the potential public health benefit vaccination would provide.

GARDASIL® induced robust immune response in all populations studied. Based on the numerically superior and statistically non-inferior anti-HPV responses induced by GARDASIL® in 9 to 15 year-old boys compared with 16 to 26 year-old men, the efficacy of GARDASIL® can be bridged from men in whom efficacy was demonstrated to boys in whom efficacy studies were not feasible.

The clinical program also has shown that GARDASIL® is generally well-tolerated when administered to males 9-26 years of age. No vaccine-related serious adverse experiences were reported in males. Compared with placebo recipients, a slightly higher proportion of vaccinees reported injection site and systemic adverse experiences, the majority of which were reported as mild to moderate intensity. The proportions of subjects reporting new medical conditions were similar between GARDASIL® and placebo recipients. Overall, the safety profile observed in male studies is comparable to the safety profile of GARDASIL® in females.

This briefing document provides an overview of the unmet medical need related to HPV-associated infection and diseases in males and the data on safety, immunogenicity, and efficacy of GARDASIL® when administered to boys and men 9-26 years of age. The totality of data presented in this document indicates that the overall benefit-risk profile in boys and men is favorable and supports broadening the GARDASIL® indication to males. In addition to a direct benefit to men, GARDASIL® vaccination could provide benefit to women through potentially impacting disease transmission. A mathematical model indicates that broadening the current GARDASIL® recommendation to boys and men 9 to 26 years of age would further decrease the cumulative number of genital wart cases, CIN cases, cervical cancer cases, and cervical cancer deaths in the United States by approximately 1,900,000, 270,000, 5000, and 1000, respectively, within 50 years following the introduction of the vaccine.

A Supplemental Biologics Licensing Application (sBLA) was filed by Merck & Co., Inc. on 18-Dec-2008 for use of GARDASIL® in males. The proposed prescribing information is:

- GARDASIL® is indicated in boys and men 9 through 26 years of age for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11.

2. Introduction

GARDASIL® (human papillomavirus [Types 6, 11, 16, 18] recombinant vaccine) is a vaccine intended to prevent anogenital cancer and it's precursor lesions, genital warts, and infection caused by the human papillomavirus types 6, 11, 16, and 18. These HPV types cause the majority of genital HPV disease in the United States.

To date, the clinical development program for GARDASIL® has already shown that administration of the vaccine is generally well tolerated in: (1) 9 to 15 year-old adolescents; (2) 16 to 26 year-old women; and (3) 27 to 45 year-old women. Efficacy against cervical, vulvar, and vaginal cancer caused by HPV types 16 and 18, as well as genital warts caused by HPV types 6 and 11 have been proven in 16 to 26 year-old women. Immunobridging studies among females have shown that immune response to GARDASIL® among girls aged 9-15 years is non-inferior to that observed in women for whom efficacy has been proven.

A sBLA for the use of GARDASIL® was filed by Merck & Co., Inc. in December 2008 for the indication in boys and men 9-26 years of age. The data presented in this briefing document support the proposed indication of use of GARDASIL® in boys and men 9 through 26 years of age for the prevention of genital warts (condyloma acuminatum) caused by HPV types 6 and 11.

3. Background

3.1 HPV Virology

The HPV family consists of over 100 related epitheliotropic viruses. The virus life cycle is dependent on the differentiation of epithelial cells. Cells within the anogenital epithelial layer are in a constant cycle of growth, differentiation, death, and shedding. Epithelial cells originate in the basal cell layer and gradually differentiate as they progress through the full thickness of the epithelium. On reaching the epithelial surface, terminally differentiated cells desquamate and are replaced by cells from below.

The primary target of HPV infection is the basal cell of the epithelium. Viral DNA synthesis occurs in immature basal cells, whereas, viral assembly occurs only in terminally differentiated squamous cells. Virus shedding occurs through the routine desquamation of dead epithelial cells [1].

HPV is a small, nonenveloped icosahedral capsid virus containing double-stranded DNA [2]. The viral genome is made up of 7000 to 8000 base pairs composed of early transcribed open reading frames, two late open reading frames, and a noncoding long control region. The E6 and E7 viral proteins are the most important genes from a pathophysiologic perspective. These proteins disrupt normal cell cycle control of infected cells [3]. All HPV types cause proliferation of infected cells.

Although all HPV appear to disrupt the cell cycle regulator mechanisms, true oncogenic potential is limited to a subset of HPV types. HPV types have therefore been classified as high risk (e.g., HPV 16, HPV 18, and HPV 45) and low risk (e.g., HPV 6, HPV 11, HPV 42, HPV 43, and HPV 44) [4].

The malignant phenotype of HPV 16 and HPV 18 are associated with the long duration of infection in both men and women. In both genders, HPV 16 and 18 cause approximately 75% and 5% of anal cancers, respectively. Of HPV-related penile and oropharyngeal cancers, 60-95% have been associated with HPV 16/18. HPV 6 and HPV 11 are the most common low-risk HPV types, causing 80-95% of genital warts [5]. These types are also the primary cause of recurrent respiratory papillomatosis (RRP) [6].

A vaccine that prevents infection and disease caused by HPV 6, 11, 16, and 18 will greatly reduce the burden of HPV disease in men.

3.2 GARDASIL® - Quadrivalent HPV (Types 6, 11, 16, 18) Vaccine

GARDASIL® is prepared from the highly purified virus-like particles (VLPs) of the recombinant major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The VLPs are adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant. Each 0.5-mL dose is formulated to contain 20 μg HPV 6 L1 protein, 40 μg HPV 11 L1 protein, 40 μg HPV 16 L1 protein, and 20 μg HPV 18 L1 protein. The quadrivalent final container product is a sterile suspension for injection in a single-dose vial or a prefilled syringe. For each image, the fill volume permits intramuscular injection of 0.5 mL of vaccine. GARDASIL® is not a live virus vaccine; it contains no viral DNA, and is incapable of causing infection.

3.3 Summary of Clinical Trial Findings on GARDASIL® Use in Females

GARDASIL® is a prophylactic HPV vaccine licensed for prevention of cervical, vulvar, and vaginal cancers, genital warts, and other common HPV-related genital lesions in 9 to 26 year-old girls and women. High-grade cervical, vulvar, and vaginal intraepithelial neoplasia [i.e. cervical intraepithelial neoplasia (CIN) 2/3, vulvar intraepithelial neoplasia (VIN) 2/3, and vaginal intraepithelial neoplasia (VaIN) 2/3] and adenocarcinoma in-situ (AIS) are the immediate and obligate precursors of squamous cell carcinoma of the respective anatomic areas. In prior studies, administration of GARDASIL® to 16 to 26 year-old women was shown to be highly efficacious in preventing HPV 16- and HPV 18-related cervical, vulvar, and vaginal cancers and cervical, vulvar, and vaginal pre-cancerous lesions (CIN 2/3 and AIS; VIN 2/3, and VaIN 2/3, respectively); HPV 6-, 11-, 16-, and 18-related cervical, vulvar, and vaginal dysplasia (CIN [any grade] or AIS; VIN, VaIN); and HPV 6- and 11-related condyloma acuminata.

GARDASIL® induced robust anti-HPV immune response in girls and women 9-26 years of age. Based on the demonstrated non-inferiority (and numerical superiority) of anti-HPV response among girls 9-15 years of age compared to that observed among women 16-26 years of age, efficacy was bridged to the HPV-naïve population among which efficacy studies were not feasible.

Administration of GARDASIL® has been shown to be generally-well tolerated in all female populations in which it was evaluated. The proportions of subjects who reported

serious adverse experiences, or who discontinued due to an adverse experience were low and comparable to placebo recipients. There were slightly higher incidences of injection-site adverse experiences and low-grade fever following vaccination compared to placebo recipients.

Overall, the post licensure experience with GARDASIL® collected through passive reporting of spontaneous adverse experiences to Merck & Co., Inc. has confirmed the favorable safety profile of the vaccine, with a low proportion of reported serious adverse experiences; the benefit-risk profile for the product remains favorable. Assessment based on the Vaccine Adverse Events Reporting System (VAERS) and Vaccine Safety Datalink (VSD) project indicate that the postlicensure safety data continue to support the benefit-risk profile of GARDASIL® [7; 8; 9]. Further information on overall safety of GARDASIL® among females is provided in Section 10.

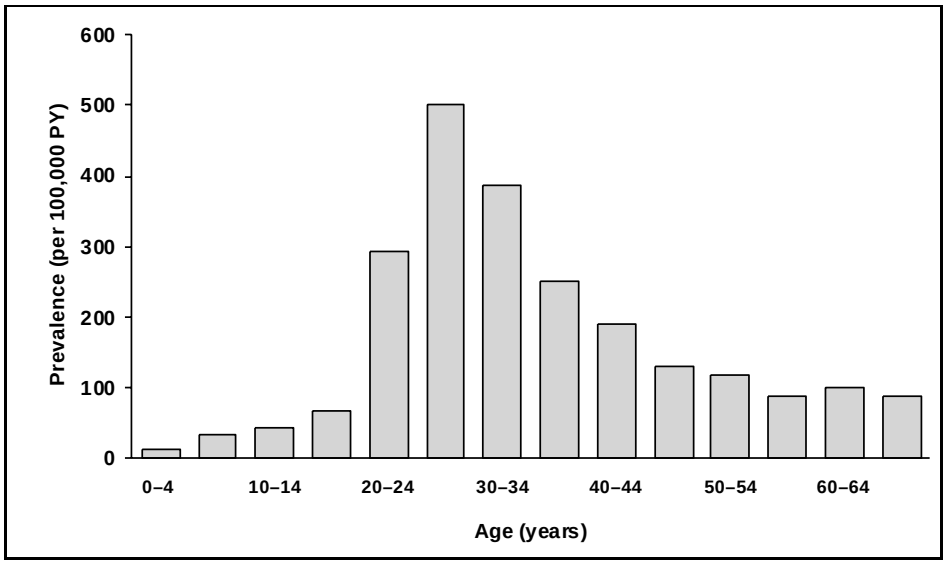
4. Unmet Medical Need - Burden of HPV in Men

HPV is one of the most common sexually transmitted infections (STI). The burden of HPV disease in men is summarized in this section. As in women, genital HPV acquisition in men generally occurs shortly after sexual debut with the acquisition of genital infection remaining relatively constant through adulthood [10]. HPV infection can result in anogenital diseases, including anogenital warts, intraepithelial neoplasia, and carcinoma of the penis and anus. These diseases are associated with substantial morbidity and mortality in men. In addition, HPV causes RRP and a sub-set of head and neck cancers. Data in this Submission focus on EGL, which are mostly external genital warts. Data on PIN or anal intraepithelial neoplasia (AIN) and associated cancers provide important supportive information, but are not the focus of this file, due to small number of PIN cases and insufficient number of AIN endpoints at this time to analyze efficacy against AIN.

Genital Warts: Condyloma acuminata, or anogenital warts, are the most common manifestation of HPV in men. Among men, about 80-95% of anogenital warts are positive for HPV 6 and/or 11 [11; 12; 13; 14; 15]. Occurrence of genital warts peaks in young adulthood in men. For example, based on private health care claims data in the United States, the highest prevalence was reported at ages 25-29 years, with prevalence of 501 per 100,000 person years (Figure 1) [16].

Figure 1

Genital Wart Prevalence Among Men by Age Group Within a Set of Private Health Plans in the United States



PY= Person years
[16]

The incidence of genital warts appears to be increasing. According to the United States National Disease and Therapeutic Index, 422,000 initial physician visits due to genital warts occurred among men and women in 2006 and 312,000 in 2007 [17]. From 1997 to 2007, the number of initial visits due to genital warts increased more than 2-fold (145,000 in 1997 and 312,000 in 2007). The age-standardized incidence of new claims due to genital warts among privately insured 15 to 59 year-old individuals in the United States increased by about 70% from 1998 (117.8 per 100,000 person years) to 2001 (205.0 per 100,000); rates increased in both genders [18].

In the GARDASIL® efficacy study in men (Protocol 020), where a diverse group of men were enrolled, the annual incidence of genital warts among HPV-naïve (PCR negative and seronegative for all 4 HPV types at baseline) HM in the placebo group was 1.0 per 100 person years, and when HPV status at baseline was not considered, incidence was 1.5 per 100 person years. Extrapolating the latter incidence rate to the United States male population of 16-26 years of age (2008 projection) suggests that approximately 350,000 new cases of genital warts occur every year among men in this age group. Among MSM in the placebo group, the incidence rate was almost three times higher (2.8 and 4.7 per 100 person years, among HPV-naïve MSM and all MSM, respectively). Furthermore, these incidence rates from Protocol 020 may underestimate the true incidence of genital warts, because men with more than 5 sexual partners before enrollment were excluded.

Based on data from Protocol 020, neither condom use nor circumcision appeared to afford full protective effect against prevalent or incident HPV infection.

Corroborating findings in the published studies, in Protocol 020 HPV 6 and 11 infections were significantly associated with development of genital warts. Of all external genital lesions, the majority of which were condyloma, 86% were HPV 6/11 positive. Within 12 months of an incident HPV 6 detection, 13.8% of HM subjects and 9.1% of MSM subjects developed an external genital wart; among subjects with incident HPV 11 detection, this progression was observed in 19.1% of HM and 21.1% of MSM.

Genital warts cause discomfort, burning, and pruritus, and are highly infectious. They can also take the more aggressive form of giant condylomata (Buschke-Lowenstein tumors). Genital warts have been shown to cause significant social stigmatization and psychosocial burden in the patients, such as anxiety [19; 20; 21].

Despite the increase in genital warts occurrence, treatments are inadequate. A myriad of treatments are available, from prescription topical agents such as imiquimod, podophyllins, to more aggressive modalities such as intralesional interferon, cryotherapy, electrocautery, laser and surgical excision. However, none of these treatments are ideal in that they carry varying degrees of risks for scarring, disfigurement, pain, and relapse. Indeed, despite treatment, condyloma can recur at a rate of 10% to 90%, varying by treatment method [22] and multiple treatments are often required. Based on claims data from privately insured male patients in the United States, on average, genital wart episodes last 102.6 days [95% confidence interval (CI): 77.8–127.4], and patients have 3.1 physician visits (95% CI: 2.8-3.5), with an estimated total health care cost of $477 (95% CI: $365–$590) per episode [16]. Costs increase significantly for men with more recalcitrant cases of HPV infection, where repeat electro-, laser-, or cryosurgery or intralesional interferon may be required. Costs of intralesional interferon can exceed the $2000-5000 [23] and the side effects include constitutional symptoms such as fever and malaise.

Conservative estimates of annual United States national direct medical costs due to anogenital warts among both men and women have ranged between approximately $170 million and $225 million [24]. These estimates have not included health care visits that take place outside the health care systems analyzed (i.e. physicians with private practice or providers of privately insured patients), such as STD clinics, family planning and college student health clinics. The indirect costs of social stigmatization and psychosocial burden are also not factored into these estimates. Studies of indirect costs related to anogenital warts are not available meaning the true economic burden of genital warts is probably considerably higher than what has been estimated; however, the extent of actual difference is unknown. Therefore, these figures underestimate the true burden of genital warts.

Genital warts comprise the most common EGL identified in Protocol 020, and compelling data on vaccine efficacy are included in this application. However, HPV infection is associated with a variety of other conditions, including premalignant and malignant neoplasms, as well as other conditions such as RRP. While only limited or no data are provided in this application to support a role for vaccine efficacy in these

conditions, these conditions (outlined below) provide other potential benefits of an HPV vaccine.

Penile/Perianal/Perineal Cancer: In high-income countries, penile cancer is a relatively rare disease, but is associated with considerable morbidity and mortality in the patients. About 40-50% of penile cancer is related to HPV [25], similar to what has been reported for vulvar carcinoma. HPV 16 is the most frequently identified type; HPV 16 and 18 account for greater than 60% of HPV detected [26; 27; 28; 5]. In high-income countries, reported penile cancer incidence varies between 0.3 and 2.2 per 100,000 [5]. In lower income countries, penile cancer is a larger public health problem [29; 30; 31]. It is estimated that in 2002, globally about 26,000 cases of penile carcinoma occurred, of which ~6,600 were related to HPV 16/18 [5]. In the United States, an estimated 1,250 cases and 290 deaths due to penile and other genital cancers (excluding prostate and testis) occurred in 2008 [32].

Patients with penile carcinoma seek health care later than patients with other types of cancer, due to fear, embarrassment, ignorance, and/or neglect. Start of treatment can be delayed for >1 year in up to 50% of patients [5]. In the United States, fatality has been reported as 41% [33]. Age, race, and stage of disease at diagnosis are associated with survival. Penectomy is associated with substantial sexual dysfunction and psychosocial burden [34; 35].

PIN 1 is low grade and PIN 2/3 are high grade dysplastic lesions. HPV positivity has been reported in up to 84% of PIN 1 cases [36] and over 90% of PIN 3 cases [36; 37; 38]. HPV 16 is the most common type detected. Erythroplasia of Queyrat (EQ), Bowen's disease (BD), and Bowenoid papulosis (BP) are clinical presentations of high-grade PIN. As many as 33% of BD and EQ, has been known to progress to invasive cancer [39; 40].

Anal Cancer: Globally, 40,000 new cases of anal cancer in men were estimated in 2002 [27]. In the United States, an estimated 2,020 new cases and 250 deaths due to cancers of anus, anal canal and anorectum occurred in men in 2008 [32]. Studies suggest that anal cancer incidence has been increasing in several parts of the world [41; 42]. In the United States, age-adjusted incidence of invasive anal cancer among men increased from 0.97 per 100,000 population in 1973-1979 to 1.59 per 100,000 population in 1994-2000, representing a 64% increase in ~2 decades [42].

MSM and human immunodeficiency virus (HIV) infected individuals are at higher risk of developing anal cancer than HIV uninfected individuals. Before the HIV epidemic, incidence of anal cancer among MSM was estimated as 35 per 100,000, similar to cervical cancer rates before introduction of cervical screening [43]. In the highly active anti-retroviral therapy era, the incidence of anal cancer has not declined. Prognosis of anal cancer is poor in HIV-infected patients [44].

The great majority of anal cancers are squamous cell carcinoma (SCC) and HPV infection is strongly associated with anal cancer [45; 46; 47; 48]. Anal canal SCCs were found to be HPV positive in 75-90% of cases in men [5; 49]. HPV 16 (73%) and HPV 18 (5%) are the most commonly associated types [49]. The concept of high-grade AIN as a precursor of invasive anal SCC is supported by the association of high-risk HPV types with developing high-grade AIN, mixed lesions of coexistence of high-grade AIN with

invasive cancer, high-grade AIN showing biological and molecular characteristics that resemble anal cancer, and by prospective studies assessing progression to invasive cancer among patients with high grade AIN [50; 51; 52; 53; 54; 55].

Head and Neck Cancers: Approximately 560,000 new cases of head and neck squamous cell cancers (HNSCC) and 250,000 deaths due to HNSCC are reported annually worldwide. Overall, two thirds of HNSCC cases occur in men. Oral HPV infection and HPV type 16 L1 seropositivity have been associated with elevated risk for development of oropharyngeal squamous cell carcinomas (OPSCC), with reported odds ratios of 14 and 32, respectively [56; 57]. HPV-related head and neck cancers are predominantly OPSCC and, unlike traditional HNSCC, occur in younger men and are typically not associated with alcohol or tobacco use or poor oral hygiene. Over the past several decades, HPV-related HNSCC have been on the rise, both in terms of absolute incidence and as a proportion of overall HNSCC. It is currently estimated that HPV causes approximately 50-60% of OPSCC worldwide. Of these, HPV 16 is responsible for approximately 90% [58].

Recurrent Respiratory Papillomatosis (RRP): RRP is a rare, but severe disease that occurs both in children and adults. It is manifested by warts in the respiratory tract, most often in the larynx, and tends to recur despite repeated treatment efforts and can lead to death by blocking the airway. RRP is primarily caused by HPV types 6 and 11. Peak ages of disease occurrence are preschool age and young adulthood (20-40 years). A higher proportion of adult RRP patients are men [59].

Role of Men Transmitting HPV to Women: HPV is a sexually transmitted virus. Sexual partners infect each other and anogenital diseases caused by HPV in both men and women have been strongly associated with patient's as well as patient's partner's sexual behavior.

The role of men as vectors transmitting HPV types that can lead to cervical cancer has been suggested in several natural history studies that identified women's number of sexual partners to be associated with developing HPV infection and/or cervical neoplasia [60; 61; 62]. A study among women with cervical carcinomas and precancerous lesions suggested that these lesions may be associated with genital papillomavirus infection in their male sexual partners [63]. In addition, several studies have shown the association between men's sexual behavior and cervical cancer in their female partners, independent of sexual behavior of the women [64; 65; 66; 67; 68].

Several robust prospective studies show high HPV concordance between couples who recently became infected indicating transmission of HPV between the couples (male to female, and female to male) [69; 70; 71]. These data consistently support the sexually transmitted nature of HPV and the role of men in infecting women, who subsequently can develop HPV-related anogenital cancer and warts.

Summary and Conclusions: The HPV-related diseases above cause a substantial burden on the individuals and society due to associated medical and psychosocial problems, and financial costs. HPV is sexually transmitted, and men are the source of infection in women. Unlike in women, there is no screening method to detect HPV infections and

prevent progression of disease in men. Prevention through vaccination would be the best approach to reducing this burden in both men and women.

5. Overview of Clinical Development Plan for Use of GARDASIL® in Boys and Men

GARDASIL® has been studied in males in three (3) Phase III studies: Protocols 016, 018 and 020. In all, a total of 3097 subjects aged 9-26 years of age received GARDASIL®, and 2305 received placebo. Subjects were enrolled from a total of 23 countries in 6 continents, encompassing a diverse population. The age range, 9 to 26 years, covers the period soon before the sexual debut through the period of peak risk for HPV infection and diseases.

An overview of the clinical development program for males is provided below: Table 1 provides a summary of studies in boys and men within the clinical program for GARDASIL®:

a. Demonstration of vaccine safety: Vaccine safety profile was studied in all three protocols (Protocols 016, 018, and 020). Standardized safety assessments were conducted across the studies in over 3000 vaccinees.

b. Demonstration of vaccine efficacy: Efficacy against HPV-related anogenital diseases and infection was evaluated in sexually-active men 16-26 years of age in Protocol 020. Men in this age group are at high risk of acquiring HPV and developing HPV-related anogenital diseases. The study included both HM (n=3457) and MSM (n=598). Primary efficacy was measured against HPV 6/11/16/18-related external genital lesions (i.e. external genital warts, PIN, and penile, perianal or perineal cancer) in the entire study population. Efficacy against HPV 6/11/16/18 related intraanal disease [AIN (including intraanal warts) or cancer] was planned to be assessed in a substudy among MSM only. This substudy efficacy analysis has not been performed yet because the number of endpoints needed was not achieved by the time primary efficacy endpoint target was reached.

The secondary objectives of the study were to assess vaccine efficacy against HPV 6/11/16/18-related: a) persistent infection and b) DNA detection at one or more visits.

c. Demonstration of immunobridging from adult to preadolescent/adolescent males: GARDASIL® is a prophylactic vaccine and provides highest benefit if administered prior to exposure to HPV. Thus, preadolescents and young adolescents are the ideal age group to target for routine immunization. However, efficacy studies among sexually-naïve adolescents are not feasible. Therefore, vaccine efficacy was bridged from the adult male population (i.e. Protocol 020) to 9 to 15 year-old HPV-naïve boys (i.e. combined data from Protocols 016 and 018) by demonstrating non-inferiority of immunogenicity in this younger age group compared to immunogenicity in adults in whom vaccine efficacy was demonstrated. This immunobridging approach is the same approach that was used to bridge efficacy from young women to adolescent girls in the original GARDASIL® application.

Sera in Protocol 020 and Protocols 016 and 018 were collected nearly 4 years apart. Therefore, in addition to the immunobridging analysis described above, sera from a random sample of 490 vaccinated subjects [240 adult men (Protocol 020) and 250 boys (Protocols 016 and 018 combined)] were tested in parallel to provide support for the comparison of immunogenicity in subjects from Protocol 020 versus Protocols 016 and 018. Among parallel tested samples, non-inferiority of immune response in boys versus men was tested in a similar manner as the full dataset.

Table 1

Summary of Studies in Boys and Men Within the Clinical Program for GARDASIL®

Study	Study Population	Male subjects			Description
		GARDASIL®	Placebo*	Total	
		n	n	n	
016 Adolescent/Adult Bridging and End-Expiry Study	10- to 23-year-old girls and women and 10- to 15-year-old boys in the United States, Latin America, Asia-Pacific, and Europe (N=3049)	508	0	508	▪ For this submission (i.e. indication for use in males) only data from boys were used: o Safety assessment o Immunogenicity assessment for formal bridging of efficacy results from 16 to 26 year-old men to preadolescent and adolescent boys
018 Adolescent Immunogenicity and Safety Study	9 to 15 year-old boys and girls in the United States, Latin America, Asia-Pacific, and Europe (N=1775)	564	275	839	▪ For this submission (i.e. indication for use in males) only data from boys were used: o Safety assessment o Immunogenicity assessment for formal bridging of efficacy results from 16 to 26 year-old men to preadolescent and adolescent boys
020 Efficacy Study in Young Men	16 to 26 year-old men in the United States, Latin America, Asia Pacific, Europe, and Africa	2025	2030	4055	▪ Efficacy assessment ▪ Safety assessment ▪ Immunogenicity assessment for formal bridging of efficacy results from 16 to 26 year-old men to preadolescent and adolescent boys
n=Total number of male subjects who received at least one dose of study vaccine. In Protocols 016, 018 and 020 respectively, 2, 3 and 10 subjects were randomized but did not receive vaccine or placebo. *In Protocol 018 non-aluminum containing placebo and in Protocol 020 aluminum-containing placebo was used.					

6. Methods

6.1 Study Population

The efficacy trial, Protocol 020, enrolled healthy young men, 16 to 23 years of age in the HM population and 16 to 26 years of age in the MSM population, without preexisting conditions that could confound the evaluation of the tolerability, immunogenicity, or efficacy profile of the GARDASIL®. The age range for MSM subjects was wider to ensure adequate and timely enrollment from this population.

This study targeted young men with a maximum of 5 female and/or male sexual partners to minimize the proportion of enrolled subjects who were HPV sero and/or PCR positive at baseline. In addition, to retain a cohort with a reasonable risk of becoming infected after the vaccination series was completed, subjects who had not had anal or vaginal intercourse were excluded. MSM who denied having had anal sex were also eligible if they had engaged in oral sex with a male partner within the past year.

In Protocol 020, subjects were examined prior to enrollment for visible signs of HPV infection. Those with lesions felt to be definitely, probably or possibly related to HPV or of unknown etiology were not randomized. Subjects were not screened for PCR or sero positivity prior to enrollment. Men were enrolled regardless of their HPV status. Thus, GARDASIL® was tested in the manner in which its post-licensure use was envisioned.

The clinical program also enrolled 9 to 15 year-old preadolescents and adolescents. This age range represents the period immediately prior to when this population is at highest risk for acquisition of HPV infection. Because GARDASIL® is intended primarily as a prophylactic vaccine, immunization programs in 9 to 15 year-old subjects who are not yet exposed to HPV will have the highest public health benefit.

6.2 Efficacy Endpoints

Protocol 020's primary efficacy endpoint is the incidence of HPV 6-, 11-, 16-, and 18-related external genital lesions (i.e. external genital warts, PIN, penile, perianal or perineal cancer). The study's secondary endpoints are the incidence of HPV 6-, 11-, 16-, or 18-related persistent infection and detection of HPV 6, 11, 16 or 18 DNA on at least 1 visit. These endpoints were chosen based on the following considerations:

- Genital warts represent the most common clinical manifestation of HPV infection in men. While these lesions are generally benign, they cause a significant amount of embarrassment, discomfort, and disruption. Furthermore, treatment of these lesions is costly, painful, and often unsuccessful in preventing recurrence. Genital warts incidence has been increasing substantially in recent years.
- Penile cancer, although a rare event, causes significant morbidity and fatality among afflicted patients. Patients with penile carcinoma seek health care later than patients with other types of cancer, due to fear, embarrassment, ignorance, and/or neglect. Start of treatment can be delayed. Penectomy is associated with substantial sexual dysfunction and psychosocial burden. High grade PIN is considered a precancerous lesion, similar to high-grade vulvar and vaginal intraepithelial neoplasia.

- Men are vectors of HPV, and a reduction of the pool of infected men may be associated with a decreased risk of CIN and cervical cancer in women. The longer the duration of infection in men, the more likely men will transmit HPV to their sexual partners. Available limited data suggest that duration of infection in men may be shorter than what was observed in women, and therefore, it is also relevant to evaluate HPV DNA detection of any duration.

6.2.1 Ascertainment of Efficacy Endpoints

For disease and infection endpoint ascertainment, subjects in Protocol 020 underwent detailed genital examination and swabbing at Day 1, and Months 7, 12, 18, 24, 30, and 36. Subjects who had external lesions considered to be HPV-related or of unknown etiology were biopsied. These design features are described below.

6.2.1.1 Endpoints of External Genital Diseases

The protocol required a detailed external genital examination using a magnifying apparatus to identify lesions. In cases in which multiple lesions suspected to be HPV related were observed, each lesion (or set of lesions) that was morphologically and/or anatomically distinct (i.e. in a noncontiguous region) was biopsied. This design feature assured maximal ascertainment of all HPV-related lesions, including settings in which a subject was infected with more than one HPV type.

Lesions that were judged by the investigator as possibly, probably or definitely HPV-related or of unknown etiology were biopsied. This design feature required that investigators were well-trained to differentiate clinical HPV disease from diseases due to other causes. While some HPV-related lesions may be missed, eliminating the need to biopsy lesions that were highly likely to be unrelated to HPV reduced the number of low-yield biopsies. Since the region of biopsy is very sensitive, and biopsy of anogenital lesions for histopathologic diagnosis is not the standard of care (even for lesions likely to be HPV-related), the balance between complete endpoint ascertainment and subject safety/exposure to unnecessary surgery was preserved.

During genital wart treatment, follow-up biopsies were to be obtained if new HPV-related lesions of differing morphology and/or differing anatomical location appeared. However, it was important to uniformly differentiate a new lesion from a recurrence of the same lesion. A recurrence was defined as the reappearance within 2 months of a lesion of similar morphology in the same anatomical location after complete resolution of the initial lesion. Such lesions were not to be biopsied. The 2-month period to define recurrence was conservative because clinical studies have shown that therapy for a single episode of genital warts requires several rounds of therapy of up to 6 months in duration [16].

Because uniform international standards for the management of condyloma acuminata or PIN do not exist, the management of confirmed HPV-related penile, scrotal, perineal/perianal lesions was based on local standards as determined by the individual study investigators. However, treatment of external genital lesions by excision was preferred with all excised tissue being submitted to the central laboratory for diagnosis. Investigators who chose to use other methods for therapy (e.g., cryotherapy, imiquimod)

for treatment of external or intraanal lesions were required to submit biopsies before the institution of therapy. Taken together, these protocol features provided flexibility to the investigator (essential in an international clinical trial, and more generally representative of "real world" conditions) while ensuring maximal ascertainment of HPV-related lesions.

6.2.1.2 Endpoints of Persistent Infection or DNA Detection at ≥1 Visits

Infection endpoints were assessed by collection of cellular specimens through gently filing skin of the external genital area with a sterile nail file followed by swabbing the same area with a wetted DACRON™ swab. Anal cellular samples for PCR testing were collected with the help of a DACRON™ swab. The sampling technique was based on findings from a pilot study conducted by Merck and published literature [72]. As HPV infection may be focal, penile (include glans and shaft), scrotal, perineal/perianal, and anal (only in MSM) areas were swabbed and tested separately and all contributed to the infection endpoints to assure complete ascertainment of HPV in the anogenital area.

The persistent infection endpoint was defined as detection of the same vaccine HPV type DNA in 2 consecutive anogenital samples collected 6 months (±1 month) apart. The 6-month visit interval was designed to ensure maximal ascertainment of persistent HPV 6, 11, 16, or 18 infection. Since the data on the duration of incident HPV 6, 11, 16, or 18 infection in men were sparse, the duration of HPV infection in women of similar age and risk profile was referenced. Since the median duration of HPV 16 infection in women is approximately 12 months, a 6-month visit interval allowed for complete ascertainment of such infections.

HPV DNA detection at ≥1 visit (i.e. of any duration) was also included for clinical endpoint evaluation, with consideration that the duration of HPV infection in men may be shorter than that in their counterpart. DNA detection endpoint was defined as HPV 6/11/16/18 DNA detection by PCR assay on an anogenital swab or biopsy sample at one or more visits. The latter endpoint, therefore, is a composite endpoint which includes cases of HPV 6/11/16/18 related disease, persistent infection, and DNA detection at a single visit.

6.2.2 Centralized Pathology Management

All biopsy specimens were processed at a single central laboratory, the Diagnostic Cytology Laboratory, Indianapolis IN, U.S.A. (referred to as the Program Central Laboratory). Histopathologic diagnosis for case management was also provided by this laboratory.

6.2.3 Pathology Panel

For endpoint assessment, all biopsy specimens were reviewed by a Pathology Panel which consisted of 4 expert pathologists. Merck Research Laboratories (MRL) and the Pathology Panel followed established guidelines for histology review. The consensus diagnoses of the Pathology Panel were used in the definition of study endpoints only.

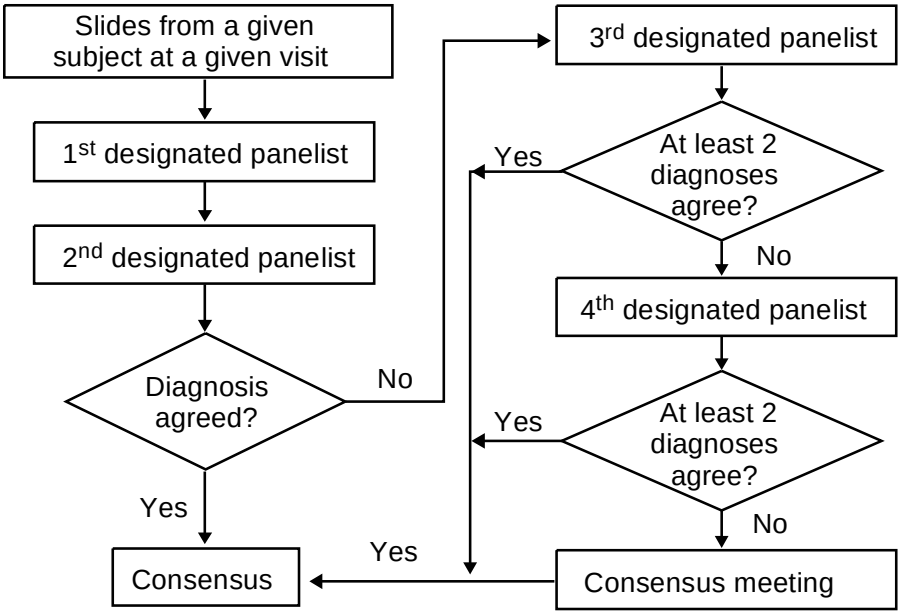
Panelists reviewed the specimen slides independently, blinded to the HPV status, central laboratory's diagnosis, other panelists' diagnoses, and other demographic and clinical data of the study subjects. The slides were reviewed first by randomly selected 2 of

4 panelists (Figure 2). If the diagnoses of the lesion made by the initial two panelists agreed, that diagnosis was considered the final consensus diagnosis with regard to the endpoint of the clinical trial. If the initial two diagnoses were discrepant, a third pathologist was called upon for the adjudication of the diagnosis, although the third panelist was not aware that he/she was a "tie-breaker". On the rare occasion that all three diagnoses were discrepant, a fourth pathologist reviewed the slides. The final diagnosis was the one rendered by two pathologists. If all four pathologists provided four different diagnoses for a given biopsy, a panel meeting consisting of all the pathologists took place to reach the final consensus (Figure 2). Overall, among the 330 EGL biopsies collected in the study, 70.0% achieved consensus diagnosis after review by two pathologists, 20.3% achieved consensus diagnosis after review by three pathologists, 9.4% achieved consensus diagnosis after review by four pathologists, and only 0.3% required a consensus meeting.

The diagnosis of the central laboratory was used for the purposes of medical management. However, if a Pathology Panel consensus diagnosis for a given specimen was deemed more severe than the diagnosis of the central laboratory for the same specimen, a written notification was sent to the study site informing them of the consensus diagnosis. Study site investigators could then use this information in determining the course of patient care.

Figure 2

Algorithm for Pathology Panel Review



6.2.4 Detection of Vaccine HPV Types in Biopsy and Swab Specimens

All biopsy and swab specimens were sent to MRL for HPV testing. Each biopsy specimen was tested by PCR for HPV, regardless of whether an HPV-related histologic diagnosis was made, for the purpose of determining the causal HPV type in the lesion. Testing was performed on thinsection microtomy specimens prepared by the Program Central Laboratory. In addition, all swab samples were tested by PCR. All laboratory staff were blinded to vaccination allocation, as well as the subject identity, visit interval, or histologic diagnosis rendered by the Program Central Laboratory or the Pathology Panel. All biopsy and Day 1 swab samples were tested for HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Swab samples collected after Day 1 were tested for HPV 6, 11, 16, and 18.

6.2.5 Disease Endpoint Adjudication

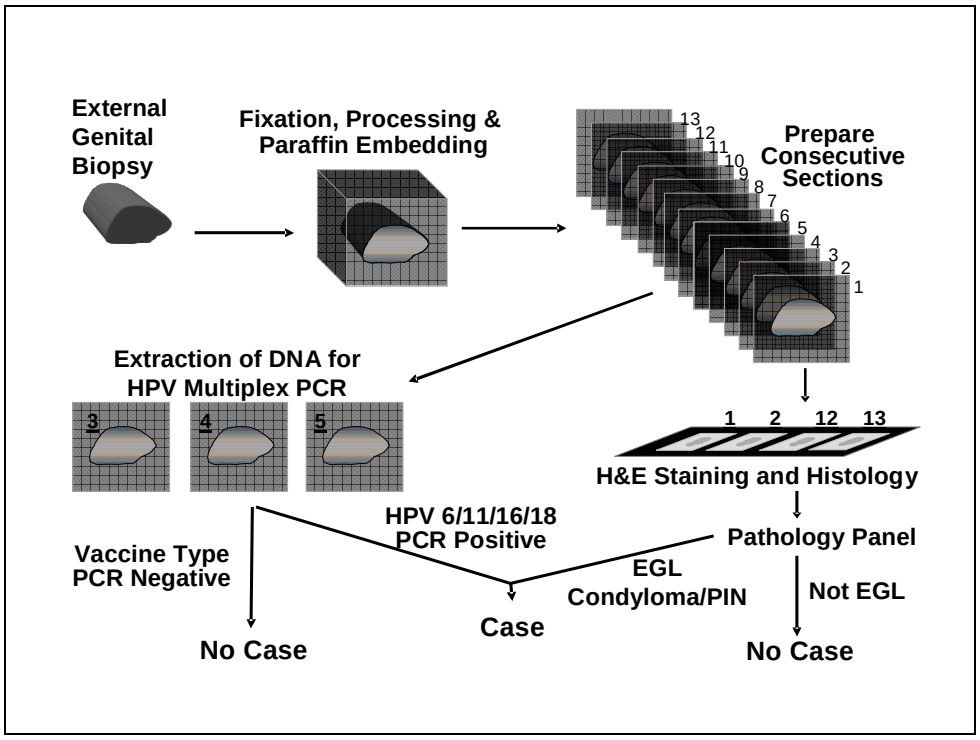
An EGL endpoint occurred if on a single biopsy or excised tissue block, the following conditions were met:

- the Pathology Panel consensus diagnosis was condylomata acuminata (genital warts), PIN 1, PIN 2/3, penile, perianal, or perineal cancer; and
- at least one of HPV types 6, 11, 16, or 18 was detected by Thinsection PCR in an adjacent section from the same tissue block.

Figure 3 provides a schematic of endpoint adjudication. Individual biopsies, collected using separate apparatus and placed into individual containers, underwent embedding and sectioning under ultraclean conditions (to minimize PCR contamination). A total of 13 sections were generated for each biopsy. The first two and last two sections were used for histologic analysis. Each of the remaining 9 sections was placed into an individual tube for PCR testing. This procedure allowed for precise co-localization of the histopathologic finding with the causal HPV type. This method ensured highly accurate assessment of the associated HPV type, as the section in which HPV testing occurred was a section adjacent to the section in which histopathology was read.

Figure 3

Detection of Study Endpoints in Biopsy Specimens in the Efficacy Trial of GARDASIL®



PCR = Polymerase chain reaction; EGL = External Genital Lesion; H&E = Hematoxylin and eosin; HPV = Human papillomavirus; DNA = Deoxyribonucleic acid

6.3 Immunogenicity Assays

The clinical trials program for GARDASIL® evaluated vaccine-induced immune responses. Evaluation was conducted at the completion of the vaccination regimen (1 month post-dose 3) and for up to 1.5 years thereafter in 16 to 26 year-old men and 9 to 15 year-old boys. Immunogenicity endpoints for clinical trials were: (1) anti-HPV geometric mean titers (GMTs), which is a standard summary measure of immunogenicity; and (2) the proportions of subjects who seroconverted to each HPV type four weeks post-dose 3

(assay-defined serostatus cutoff titers for each vaccine HPV type were: ≥20 milli-Merck Units per milliliter [mMU/mL] for HPV 6, ≥16 mMU/mL for HPV 11, ≥20 mMU/mL for HPV 16, and ≥24 mMU/mL for HPV 18). The minimum anti-HPV levels required to protect against acquisition of HPV infection has not been defined.

Competitive Luminex Immunoassay (cLIA) to Measure Serum Anti-HPV 6, Anti-HPV 11, Anti-HPV 16, and Anti-HPV 18 Responses: Vaccine-induced immune responses were measured in a Luminex-based format in all studies among males. Results for the assay were reported as concentration of antibody in mMU/mL. To define the serostatus cutoff, the positivity rates for ~500 samples were assessed at 11 different cutoffs. Prior to testing, sera were classified into panels according to their potential for being a true positive based on clinical history and PCR test results.

6.4 Evaluations of Vaccine Safety

GARDASIL® was evaluated for: (1) injection-site and systemic tolerability, and (2) impact on long-term health status.

In all trials of GARDASIL® in boys and men, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of study vaccine. Temperature values and injection-site adverse experiences (pain, redness and swelling) were recorded for 5 days (Days 1 through 5 postvaccination), and systemic adverse experiences and any other medications administered were recorded for 15 days (Days 1 through 15 postvaccination) on the VRC by study subjects. The investigator determined seriousness, action taken, and relationship to study vaccine for any VRC-recorded adverse experience. A vaccine related adverse experience was one determined by the investigator to be possibly, probably or definitely related.

In all clinical trials of GARDASIL®, investigators were instructed to report any serious adverse experience (SAE) occurring in any subject from the time the consent form was signed through 14 days following the first vaccination and from the time of any subsequent vaccination through 14 days thereafter, whether or not the serious adverse experience was vaccine related. In addition, at any time during the study, if the event was considered by the investigator to be vaccine related or related to a study procedure, it was to be immediately reported. Death due to any cause and discontinuation due to an adverse experience was reported at any time during the study.

In all trials, subjects were evaluated for new onset medical conditions for the duration of the study. Medical History at Day 1 was recorded for all subjects. Any acute or chronic medical conditions that occurred during the year prior to study entry were recorded. After Day 1, any medical history or conditions or procedures that occurred since the last study visit were recorded. New medical conditions were not considered adverse experiences when they occurred outside the safety follow-up period (Day 1 through Month 7) and/or were not considered by the study investigators to be vaccine/placebo related.

6.5 Statistical Methods

Statistical analyses for each clinical study were prespecified in Statistical Analysis Plans (SAPs). All analyses were performed according to standardized and validated methods.

Protocol 020 followed a fixed-case study design whereby statistical analyses were to be performed when a prespecified number of cases had been observed. Analyses were to be performed after 32 cases of the primary endpoint (HPV 6/11/16/18-related EGL) had occurred in the per-protocol population. The substudy (anal disease) of Protocol 020 also followed a fixed-case study design and analyses were to be performed after 17 cases of the substudy endpoint (HPV 6/11/16/18-related AIN and anal cancer) had occurred in the MSM per-protocol population. At the time of database lock for the Protocol 020 primary efficacy analysis, which included data collected through the visit cut-off date of 29-Aug-2008, there were 34 cases of 6/11/16/18-related EGL reported in the per-protocol population. As the case target of 17 was not met for the MSM substudy endpoint, the substudy analysis was not performed.

Follow-up is continuing in Protocol 020 to obtain greater precision in the estimation of the primary study endpoint and to accrue more cases of the MSM substudy endpoint.

6.5.1 Definition of Populations Used in Analyses

Three different populations were used in vaccine efficacy analyses in Protocol 020, which include the per-protocol efficacy (PPE) population, generally HPV naïve (GHN) population, and full analysis set (FAS). The key elements for the populations used in prophylactic efficacy analyses are summarized in Table 2. The key elements for the populations used in population benefit analyses are summarized in Table 3.

6.5.1.1 Populations Used in Prophylactic Efficacy Analyses

Two populations were used in assessing prophylactic efficacy of GARDASIL® in Protocol 020: PPE and FAS. The primary efficacy analysis for the prophylactic efficacy of GARDASIL® utilized the PPE population since this allowed measurement of the full benefit of the vaccine in persons who were naïve to the relevant vaccine HPV type through the completion of 3-dose vaccination regimen. Full vaccine benefit is not expected until after the 3-dose vaccination series is completed (i.e. starting after 4 weeks following dose 3).

Analyses in the FAS population were supportive of the primary analysis in the PPE population. Compared with the main analysis populations, the FAS also included subjects who had prior exposure or were currently infected with a vaccine or non-vaccine HPV type at Day 1. Because this population includes virtually everyone in the study, the FAS approximates the general population of sexually-active 16 to 26 year-old men. Evaluating prophylactic efficacy impact was measured on vaccine-type disease only (and hence representing a mix of prevalent and incident vaccine-type disease, only the latter of which would be expected to be affected by GARDASIL®). This analysis shows vaccine impact on vaccine type EGL in the general population of 16 to 26 year-old men, starting immediately after the first dose.

6.5.1.2 Populations Used in Population Benefit Analyses

The analysis of efficacy with respect to the population benefit endpoints (i.e. evaluation of the impact of GARDASIL® on the incidence of disease caused by vaccine and non-vaccine HPV types and external genital procedures and therapies) was performed among the GHN and the FAS.

The GHN population was designed to approximate a population of adolescent and young adult men who were either sexually-naïve or sexually-experienced and had not yet been exposed to *any* HPV type. Given that it is impossible to evaluate GARDASIL® in boys prior to sexual debut (i.e. the intended target for vaccination), the SPONSOR believes that the GHN population is the correct subpopulation in Protocol 020 to provide insight on the potential population benefit of vaccination on males when vaccinated in young adolescence, prior to HPV exposure.

As mentioned previously, FAS represents the general population of sexually-active 16 to 26 year-old men. Different from prophylactic efficacy, when evaluating population benefit on overall EGL reduction, impact on endpoints due to *any* HPV type (both vaccine and non-vaccine types, both prevalent and incident infection and disease) was measured, with only the incident vaccine type disease anticipated to be substantially affected by the GARDASIL®.

Table 2

Definitions of Populations Used in Prophylactic Efficacy Analyses in Protocol 020

Parameter	**PPE**	**FAS**
Definition	Per-protocol efficacy (PPE): Included subjects who: (1) were sero- and PCR-negative at Day 1 and PCR-negative through Month 7 to the appropriate vaccine HPV types; (2) received all 3 vaccinations within a one year period; and (3) generally did not deviate from the protocol.	Full analysis set (FAS): Included all subjects who received at least 1 vaccination.
Case Counting	Cases were counted starting after Month 7.	Cases were counted starting after Day 1.
Relevant Endpoints	HPV 6-, 11-, 16-, and 18-Related External Genital Lesions HPV 6-, 11-, 16-, and 18-Related Persistent Infection HPV 6-, 11-, 16-, and 18-Related DNA Detection	HPV 6-, 11-, 16-, and 18-Related External Genital Lesions HPV 6-, 11-, 16-, and 18-Related Persistent Infection HPV 6-, 11-, 16-, and 18-Related DNA Detection
Role in the Analysis Plan	Primary efficacy analysis population.	Supportive to primary efficacy analysis.
Value of Population in Evaluating Vaccine Efficacy	Measurement of the full benefit of GARDASIL® in persons who were naïve to the relevant HPV type through the completion of 3-dose vaccination regimen.	Measurement of vaccine impact on vaccine type EGL in the general population of 16 to 26 year-old men, starting immediately after the first dose.
DNA = Deoxyribonucleic acid: HPV = Human papillomavirus; PCR = Polymerase chain reaction; EGL = external genital lesions		

Table 3

Definitions of Populations Used in Population Benefit Analyses in Protocol 020

Parameter	GHN	FAS
Definition	Generally HPV-naïve (GHN): Included all subjects who: (1) were seronegative and PCR negative to all 4 vaccine HPV types at Day 1; (2) were PCR negative to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, *and* 59 at Day 1; (3) for MSM subjects, had a Pap test result at enrollment that was negative for SIL; and (4) received at least 1 vaccination.	Full analysis set (FAS): Included all subjects who received at least 1 vaccination.
Case Counting	Cases were counted starting after Day 1.	Cases were counted starting after Day 1.
Relevant Endpoints	External Genital Lesions (caused by vaccine or non vaccine HPV types) External Genital Lesion Procedures and Therapies	External Genital Lesions (caused by vaccine or non vaccine HPV types) External Genital Lesion Procedures and Therapies
Role in the Analysis Plan	Key analysis population for the evaluation of the population benefit of the GARDASIL®.	For the evaluation of the population benefit of the GARDASIL®, supportive population.
Value of Population in Evaluating Vaccine Efficacy	GHN population approximates a population of adolescent and young adult men who were either sexually-naïve or sexually-experienced and had not yet been exposed to *any* HPV type. This population provides insight on the potential impact of vaccination on males when vaccinated in young adolescence, prior to HPV exposure.	FAS population provides information on overall vaccine impact when used in a general population of sexually active 16 to 26 year-old men.

HPV = Human papillomavirus; MSM = Men having sex with men; Pap = Papanicolaou; PCR = Polymerase chain reaction; ; SIL = Squamous intraepithelial lesion.

6.5.2 Efficacy Methodology

For the primary efficacy hypothesis in Protocol 020, the statistical criterion for success required that the lower bound of the two-sided 95% confidence interval for vaccine efficacy against HPV 6/11/16/18-related EGL in the PPE population exclude 20%. In this case, vaccine efficacy is the relative risk reduction of developing an HPV 6/11/16/18-related EGL in the vaccine group compared to the placebo group. The estimate for vaccine efficacy was computed under the assumption that the number of primary efficacy cases among vaccine recipients followed a Binomial distribution given the total number of cases, which followed from an assumption that incidence rates among vaccine and placebo recipients were means of independent Poisson processes. The 95% confidence interval for vaccine efficacy was determined using exact methods. All estimates obtained were adjusted for differences in the person-years of follow-up time accrued in the vaccine and placebo groups. The success of the secondary endpoints, HPV 6/11/16/18-related persistent infection and DNA detection, required that the lower bound of the Hochberg multiplicity-adjusted two-sided confidence intervals (α=0.05) for vaccine efficacy in the PPE population exclude 20% [73]. Estimates of vaccine efficacy for the secondary endpoints were obtained using the same methods used for the primary endpoint analysis. The statistical criteria used in the study were agreed to by the FDA.

6.5.3 Immunobridging Methodology

As indicated in Section 5, efficacy studies among HPV-naïve preadolescents/adolescents are not feasible, although this age group would benefit the most from vaccination and be targeted for routine immunization. Therefore, similar to the approach taken in female studies of GARDASIL®, efficacy was bridged to preadolescents and adolescents by showing non-inferiority of immune response in the younger age group to the immune response in the adults where efficacy studies are conducted.

The hypothesis for non-inferiority at Month 7 was tested on the per-protocol immunogenicity populations from Protocols 016 and 018 (adolescents) and Protocol 020 (adults). The statistical criterion for non-inferiority of GMTs corresponds to the lower bound of the 95% confidence interval for the fold-difference in GMTs between the 2 groups, (adolescent group/adult group), excluding a decrease of 2-fold or more for each HPV type. The statistical criterion for non-inferiority of seroconversion rates corresponds to the lower bound of the 95% confidence interval for the difference in seroconversion rates between the 2 groups, (adolescent group - adult group) excluding a decrease of 5 percentage points or more for each HPV type. Success was required for each HPV type on both endpoints. Confidence intervals for GMT fold-differences were derived from Analysis of Variance (ANOVA) models (1 per HPV type) with a response of log individual titer. Confidence intervals for differences in seroconversion rates used the method of Miettinen and Nurminen [74].

7. Efficacy Results

This section describes baseline characteristics and subject accounting in vaccine and placebo groups of Protocol 020 and provides data on efficacy findings. Overall, vaccine and placebo groups were similar in terms of all baseline characteristics evaluated, and eligibility for analyses was comparable between the two groups. Protocol 020 data indicate that GARDASIL® is highly efficacious in men in preventing external genital warts and persistent infection due to HPV 6, 11, 16, or 18.

7.1 Baseline Characteristics of Subjects Enrolled in the Efficacy Trial

Table 4 summarizes important baseline characteristics of the subjects enrolled in Protocol 020 by vaccination status. Subjects randomized to vaccine or placebo groups were comparable in terms of age, race/ethnicity, region, smoking and circumcision status, age of sexual debut, and lifetime number of sexual partners.

Table 4

Summary of Selected Baseline Characteristics of Subjects by Vaccination Group - Protocol 020

	GARDASIL® (N = 2,032)	Placebo (N = 2,033)	Total (N = 4,065 †)
	n (%)	n (%)	n (%)
Age (years)			
Mean	20.6	20.5	20.5
Standard Deviation	2.0	2.0	2.0
Median	20	20	20
Range	16 to 26	15 to 27	15 to 27
Sexual Orientation			
HM	1731 (85.2)	1732 (85.2)	3463 (85.2)
MSM	301 (14.8)	301 (14.8)	602 (14.8)
Race/Ethnicity			
Asian	201 (9.9)	205 (10.1)	406 (10.0)
Black	405 (19.9)	400 (19.7)	805 (19.8)
Hispanic American	412 (20.3)	423 (20.8)	835 (20.5)
Native American	1 (0.0)	2 (0.1)	3 (0.1)
White	719 (35.4)	712 (35.0)	1,431 (35.2)
Other	294 (14.5)	291 (14.3)	585 (14.4)
Region			
Africa	268 (13.2)	270 (13.3)	538 (13.2)
Asia-Pacific	180 (8.9)	181 (8.9)	361 (8.9)
Europe	248 (12.2)	248 (12.2)	496 (12.2)
Latin America	788 (38.8)	787 (38.7)	1,575 (38.7)
North America	548 (27.0)	547 (26.9)	1,095 (26.9)
Smoking Status			
Current smoker	726 (35.7)	751 (36.9)	1,477 (36.3)
Ex-smoker	147 (7.2)	146 (7.2)	293 (7.2)
Never smoked	1,137 (56.0)	1,126 (55.4)	2,263 (55.7)
Missing or Unknown	22 (1.1)	10 (0.5)	32 (0.8)
Circumcision			
Yes	786 (38.7)	757 (37.2)	1,543 (38.0)
No	1,244 (61.2)	1,275 (62.7)	2,519 (62.0)
Missing or Unknown	2 (0.1)	1 (0.0)	3 (0.1)
Lifetime Number of Male or Female Sexual Partners‡			
1	409 (20.2)	448 (22.1)	857 (21.1)
2	384 (18.9)	408 (20.1)	792 (19.5)
3	436 (21.5)	447 (22.0)	883 (21.8)
4	425 (20.9)	364 (17.9)	789 (19.4)
5	359 (17.7)	347 (17.1)	706 (17.4)
>5	2 (0.1)	6 (0.3)	8 (0.2)
Age at First Sexual Intercourse‡			
Mean	16.8	16.8	16.8
Standard Deviation	2.1	2.2	2.2
Median	17	17	17
Range	5 to 24	5 to 26	5 to 26

† There were 10 subjects that were randomized, but never received study vaccine.
‡ Among HM who have had vaginal intercourse with a female partner and MSM who have had insertive or receptive anal intercourse with a male partner.
Percent calculated as 100*(n/N)
N = Number of subjects randomized.

Of the 4065 subjects randomized in Protocol 020, 3706 (91.2%) received 3 doses of vaccine or placebo (91.5% and 90.8% of subjects randomized to vaccine and placebo groups, respectively). At the visit cut-off date for the primary efficacy analysis, 3248 (79.9%) subjects have either completed or were continuing in the study. The proportion of subjects continuing/completed the study was similarly high in vaccine (80.0%) and placebo (79.8%) groups.

Table 5 provides the number of subjects in the PPE population eligible for each efficacy endpoint analysis. The number of subjects eligible for analyses was similar between the vaccine and placebo groups.

Table 5

Subject Accounting for the Efficacy Analysis Populations by Vaccination Group – Protocol 020

	GARDASIL® (N=2,032)	Placebo (N=2,033)	Total (N=4,065)
Number of Subjects who received at least 1 injection[†]	2,025	2,030	4,055
HPV 6/11/16/18 PPE-Eligible[‡]	1,433	1,453	2,886
With Follow-up for HPV 6/11/16/18-Related EGL	1,397	1,408	2,805
With Follow-up for HPV 6/11/16/18-Related Persistent Infection	1,390	1,400	2,790
With Follow-up for HPV 6/11/16/18-Related DNA Detection	1,390	1,400	2,790
Eligible for the PPE Analysis Related to:			
HPV 6/11	1,277	1,280	2,557
HPV 16	1,327	1,308	2,635
HPV 18	1,367	1,395	2,762
Reason for Ineligibility[§]			
General protocol violation	83	68	151
Vaccination series not completed within 12 months[‖]	7	7	14
Missed 2nd and 3rd vaccination	89	101	190
Missed 3rd vaccination	76	83	159
Without Day 1 serology results within acceptable day range[¶]	5	8	13
Without Day 1 swab PCR results within acceptable day range[#]	169	161	330
Without Month 7 swab PCR results within acceptable day range[#‖]	244	221	465
HPV 6 or 11 Positive by Serology or PCR[††]			
At Day 1	194	191	385
At or before Month 7	229	243	472
HPV 16 Positive by Serology or PCR[††]			
At Day 1	120	143	263
At or before Month 7	164	192	356
HPV 18 Positive by Serology or PCR[††]			
At Day 1	77	70	147
At or before Month 7	101	95	196

[†] Subjects who did not receive at least 1 injection were excluded from all analysis populations.
[‡] Defined as eligible for the PPE-analysis related to any of the HPV types 6, 11, 16, or 18.
[§] Subjects are counted once in each applicable exclusion category. A subject may appear in more than one category.
[‖] Among subjects who received all 3 vaccinations.
[¶] Includes subjects with a missing serum sample or missing cLIA results for ≥ 1 HPV type.
[#] Includes HM subjects who are missing at least two required swab samples or PCR results for ≥ 1 HPV type and MSM subjects who are missing at least three required swab samples or PCR results for ≥ 1 HPV type.
[††] Day 1 includes seropositivity or PCR positivity. Post-Day 1 includes PCR positivity only. Applies only to the analysis populations for the respective HPV type(s).
N = Number of subjects randomized to the respective vaccination group.
cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; PCR = Polymerase chain reaction; PPE = Per-Protocol efficacy; DNA = Deoxyribonucleic acid; EGL = External genital lesions with a diagnosis of Condyloma Acuminata, PIN, or Penile/Perianal/Perineal Cancer; HPV = Human papillomavirus;

7.2 Subjects Excluded from Analyses:

A total of 11 allocation numbers associated with 6 subjects were excluded from all analyses (including baseline characteristics) in Protocol 020. These incidents occurred in 2 sites out of 69 sites in the study. Four of these subjects enrolled more than once and the original 4 allocation numbers and their subsequent 5 allocation numbers were excluded. An additional 2 subjects were also excluded from analyses, as non-study participants presented to the study site in place of them. None of these subjects had biopsy specimens collected. PCR data from these subjects indicate that none had HPV 6/11/16/18-related persistent infection. Of these subjects, only one placebo recipient was eligible to be a case of HPV 6/11/16/18-related DNA detection.

7.3 Efficacy With Respect to HPV 6-, 11-, 16-, and 18-Related Disease and Infection

Protocol 020 demonstrated high efficacy of GARDASIL® in preventing HPV 6/11/16/18-related EGL and the primary objective was achieved. The vaccine efficacy against HPV 6/11/16/18-related EGL was 90.4% (95% CI: 69.2, 98.1) (Table 6). Analysis was conducted in the PPE population, the predefined primary population for efficacy, and success was achieved in the test of the primary efficacy hypothesis with a p-value < 0.001.

Out of 34 HPV 6/11/16/18-related EGL cases in the PPE population, 31 were cases of external genital warts (condyloma acuminata). There were 3 cases of condyloma acuminata among the vaccinated group versus 28 cases in the placebo group in the PPE population (Table 6) and all were associated with either HPV 6 and/or 11. Only 2 cases of genital warts in the PPE population were associated with HPV 16 and 18; both were co-infected with HPV 6. Vaccine efficacy against HPV 6/11-related condyloma acuminata was 89.3% (95% CI: 65.6, 97.9).

There were 3 cases of HPV 6/11/16/18-related PIN in the PPE population; none were among vaccinated subjects. No cases of cancer were detected during the study. Although vaccine efficacy against HPV 6/11/16/18-related PIN 1 or worse diagnoses was 100% (95% CI: -141.2, 100), the small number of cases preclude a definitive empirically-supported conclusion.

Figure 4 shows the cumulative incidence over time for HPV 6/11/16/18-related EGL by vaccination group in the PPE population. This plot is truncated at Month 30 due to limited follow-up information beyond this time point since the study is still ongoing. While the incidence rate in the placebo group increased during the entire duration of follow-up shown, the incidence rate in the vaccine group remained low indicating persisting vaccine-induced protection against HPV 6/11/16/18 related EGL through approximately 3 years after onset of vaccination.

With respect to the secondary efficacy endpoints, the vaccine efficacy against HPV 6/11/16/18-related persistent infection was 85.6% (97.5% CI: 73.4, 92.9) and against HPV 6/11/16/18-related DNA detection at ≥1 visits was 44.7% (95% CI: 31.5, 55.6) (Table 6). Success was achieved in the test of both secondary hypotheses with p-values < 0.001.

GARDASIL® was highly efficacious against persistent infection due to any of the four HPV types included in the vaccine. Both in men and women, persistent infection has been associated with development of disease. In Protocol 020, persistent infection with HPV 6/11 was a significant predictor of condyloma acuminata, and HPV 6/11/16/18-related persistent infection was a significant predictor of PIN, bearing in mind that the number of PIN cases in the analysis was small. Although efficacy against HPV 16- or 18-related EGL could not be proven due to the small number of cases and an indication for these lesions are not being sought, high efficacy against HPV 16- or 18-related persistent infection suggest the potential to prevent development of genital diseases (high-grade precancerous lesions or cancers) related to these high-risk HPV types.

Efficacy against the DNA detection endpoint indicates that GARDASIL® reduces HPV 6/11/16/18 DNA detection at ≥1 visits (i.e. any duration) by 45%. This endpoint includes cases of persistent infection, as well as cases with DNA detection at a single visit. Efficacy against persistent infection was demonstrated to be high (i.e. 86%). It is unknown whether cases of single time DNA detection without persistent infection have true HPV infection or a temporary deposition from a recent sexual encounter. The vaccine is not expected to have efficacy against deposition. This may be the reason for the lower efficacy estimate observed against DNA detection of any duration.

The supportive analysis in the FAS population (Table 7), including analysis for HPV 6/11-related genital warts, was consistent with the primary analysis in the PPE population and supports the conclusion that GARDASIL® is efficacious in males in preventing HPV 6/11/16/18-related EGL and HPV 6/11-related genital warts. As was the case in the studies in women, the inclusion of endpoints caused by prevalent infections that were present at vaccination onset (endpoints that will not be impacted by prophylactic vaccines such as the GARDASIL®) reduced the estimate of vaccine efficacy.

Figure 5 displays the cumulative incidence of HPV 6/11-related genital warts among the FAS population. Data show that efficacy of the GARDASIL® emerges soon after the vaccination series is completed. Across the study duration, cumulative incidence in placebo subjects increased and in vaccinees the rates remained significantly lower than in the placebo group.

Similarly, analysis of efficacy against HPV 6/11/16/18 related persistent infection or DNA detection in the FAS population was supportive of the analysis in the PPE population, indicating the overall benefit of vaccination among males in this study. As with the primary analysis, the inclusion of endpoints caused by prevalent infections that were present at vaccination onset reduced the estimate of vaccine efficacy.

7.4 Population Benefit - Overall Rates of Genital Disease and Related Procedures and Therapy

The public health benefit of GARDASIL® in males will come through the vaccine's impact on a man's risk for developing genital warts, penile, perineal, perianal neoplasia and cancer and the public health burden related to treating these clinical HPV diseases. Regarding clinical HPV diseases, this submission focuses primarily on EGL, as there are

limited or no data available on precancerous or cancerous lesions. Therefore, population benefit is measured through assessing impact of GARDASIL® on reducing incidence of EGL due to any HPV type and incidence of external genital procedures and therapies. Impact is assessed on two study populations which represent different male populations in real life that could be targeted for vaccination. The first population is GHN; which is designed to approximate a population of adolescent and young adult men who are either sexually-naïve or sexually-experienced but not yet exposed to *any* HPV type tested (i.e. HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59). The second population is the FAS; it approximates the general population of sexually-active 16 to 26 year-old men, being a combination of both HPV- infected and uninfected individuals.

Results of analyses of efficacy against EGL due to any HPV type are in Table 8. In the GHN population, the vaccine efficacy for EGL due to any HPV type was 83.8% (95% CI: 61.2, 94.4), signifying efficacy of GARDASIL® in reducing the incidence of overall EGL in the population that approximates HPV-naïve adolescents or young adult men. Efficacy against EGL due to any HPV type is expected, since vaccine HPV types are the predominant types in EGL.

The vaccine efficacy against EGL due to any HPV type was 60.2% (95% CI: 40.8, 73.8) in the FAS (Table 8). Due to EGL occurring as a result of infections present at the onset or incident in the early phase of vaccination series, vaccine efficacy in this population is expected to be lower than the GHN population. However, the observed efficacy against EGL due to any HPV type in the FAS highlights the benefit of vaccinating a general population of 16- to 26-year-old men, even though they may be sexually active. Furthermore, the efficacy would increase and the vaccine impact would be more apparent over time, as new vaccine-type infections are prevented beginning after the 3-dose vaccination regimen is completed.

Results of analyses of the impact of GARDASIL® on the incidence of external genital procedures and therapy are in Table 9. EGL therapies in this analysis include all therapies that could potentially be associated with HPV-related EGL (i.e. surgical therapies included procedures such as surgical excision, laser ablation, cauterization, coagulation, and cryotherapy, and non-surgical therapies included topical treatments, including chemical ablation). In addition, investigators were instructed to collect biopsies from any lesion that could possibly, probably or definitively be associated with HPV or whose relationship to HPV could not be determined, to increase sensitivity of EGL detection. Therefore, these procedures and therapies are not necessarily associated with a diagnosis of condyloma acuminatum or PIN (as determined by the pathology panel), or detection of HPV in the lesion. As they may include therapies or procedures that are associated with non-HPV related EGL or other external genital diseases, the specificity of these endpoints and vaccine efficacy estimates for them are expected to be lower than what has been observed against vaccine type HPV-related EGL.

In both the GHN population and the FAS, there were substantial reductions in the incidence of external genital biopsies, external genital therapies overall, and surgical external genital therapies in the GARDASIL® group compared to the placebo group. Vaccine efficacy against external genital therapies was 47.9% (95% CI: 18.1, 67.5) in the GHN population and 37.6% (95% CI: 18.2, 52.6) in the FAS. For external genital biopsies, vaccine efficacy was 57.0% (95% CI: 31.3, 73.7) in the GHN population and 45.5% (95% CI: 27.9, 59.1) in the FAS. The data indicate the potential benefit of GARDASIL® vaccination in the reduction of therapies for external genital lesions and the cost associated with them. Population impact related to biopsy endpoint may vary depending on whether biopsying for diagnosis of genital lesions is the local standard of practice.

Table 6

Analysis of Efficacy of GARDASIL® in the PPE Population - (Protocol 020)

	GARDASIL® (N=2,025)				Placebo (N=2,030)						
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	CI[†]	P-value[‡]
HPV 6/11/16/18-Related EGL	1,397	3	2,830.9	0.1	1,408	31	2,812.2	1.1	90.4	(69.2, 98.1)	< 0.001
HPV 6/11-Related Condyloma acuminatum	1,245	3	2,562.3	0.1	1,244	28	2,547.8	1.1	89.3	(65.5, 97.9)	
HPV 6/11/16/18-Related EGL By Lesion Type											
Condyloma acuminatum	1,397	3	2,830.9	0.1	1,408	28	2,813.9	1.0	89.4	(65.5, 97.9)	
PIN 1 or worse	1,397	0	2,833.3	0.0	1,408	3	2,824.5	0.1	100	(-141.2, 100)	
PIN 1	1,397	0	2,833.3	0.0	1,408	2	2,826.0	0.1	100	(-431.1, 100)	
PIN 2/3 or Cancer	1,397	0	2,833.3	0.0	1,408	1	2,824.7	0.0	100	(-3788.2, 100)	
PIN 2/3	1,397	0	2,833.3	0.0	1,408	1	2,824.7	0.0	100	(-3788.2, 100)	
Penile/Perianal/Perineal Cancer	1,397	0	2,833.3	0.0	1,408	0	2,826.2	0.0	NA	NA	
HPV 6/11/16/18 Related EGL By HPV Type											
HPV 6-Related EGL	1,245	3	2,562.3	0.1	1,244	19	2,553.8	0.7	84.3	(46.5, 97.0)	
HPV 11-Related EGL	1,245	1	2,563.7	0.0	1,244	11	2,552.6	0.4	90.9	(37.7, 99.8)	
HPV 16-Related EGL	1,295	0	2,644.0	0.0	1,271	2	2,586.2	0.1	100	(-420.8, 100)	
HPV 18-Related EGL	1,335	0	2,723.3	0.0	1,354	1	2,726.6	0.0	100	(-3804.6, 100)	
HPV 6/11/16/18-Related Persistent Infection By HPV Type	1,390	15	2,549.4	0.6	1,400	101	2,469.3	4.1	85.6	(73.4, 92.9)	< 0.001
HPV 6-Related Persistent Infection	1,239	4	2,320.2	0.2	1,238	33	2,296.6	1.4	88.0	(66.3, 96.9)	
HPV 11-Related Persistent Infection	1,239	1	2,322.6	0.0	1,238	15	2,315.1	0.6	93.4	(56.8, 99.8)	

Analysis of Efficacy of GARDASIL® in the PPE Population - (Protocol 020) (Cont.)

	GARDASIL® (N=2,025)				Placebo (N=2,030)						
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	CI[†]	P-value[‡]
HPV 16-Related Persistent Infection	1,290	9	2,382.4	0.4	1,264	41	2,312.9	1.8	78.7	(55.5, 90.9)	
HPV 18-Related Persistent Infection	1,327	1	2,461.9	0.0	1,347	25	2,453.5	1.0	96.0	(75.6, 99.9)	
HPV 6/11/16/18-Related DNA Detection	1,390	136	2,455.3	5.5	1,400	241	2,404.1	10.0	44.7	(31.5, 55.6)	< 0.001
By HPV Type											
HPV 6-Related DNA Detection	1,239	51	2,292.4	2.2	1,238	99	2,267.7	4.4	49.0	(27.9, 64.4)	
HPV 11-Related DNA Detection	1,239	16	2,311.7	0.7	1,238	37	2,300.5	1.6	57.0	(20.7, 77.6)	
HPV 16-Related DNA Detection	1,290	62	2,337.7	2.7	1,264	103	2,287.8	4.5	41.1	(18.5, 57.7)	
HPV 18-Related DNA Detection	1,327	25	2,441.3	1.0	1,347	66	2,440.6	2.7	62.1	(39.2, 77.1)	

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one sub-category as he may have more than one lesion or multiple HPV types may be found in a lesion.

[†] A 97.5% CI is reported for the HPV 6/11/16/18-related persistent infection endpoint. For all other analyses, a 95% CI is reported. The CI reported for the HPV 6/11/16/18-related persistent infection endpoint differs from the other analyses due to the Hochberg multiplicity adjustment applied.

[‡] A p-value<0.025 (one-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 20% and supports the conclusion that the vaccine is efficacious against the given endpoint. The Hochberg multiplicity adjustment has been applied to the p-value reported for the HPV 6/11/16/18-related persistent infection and HPV 6/11/16/18-related DNA detection endpoints.

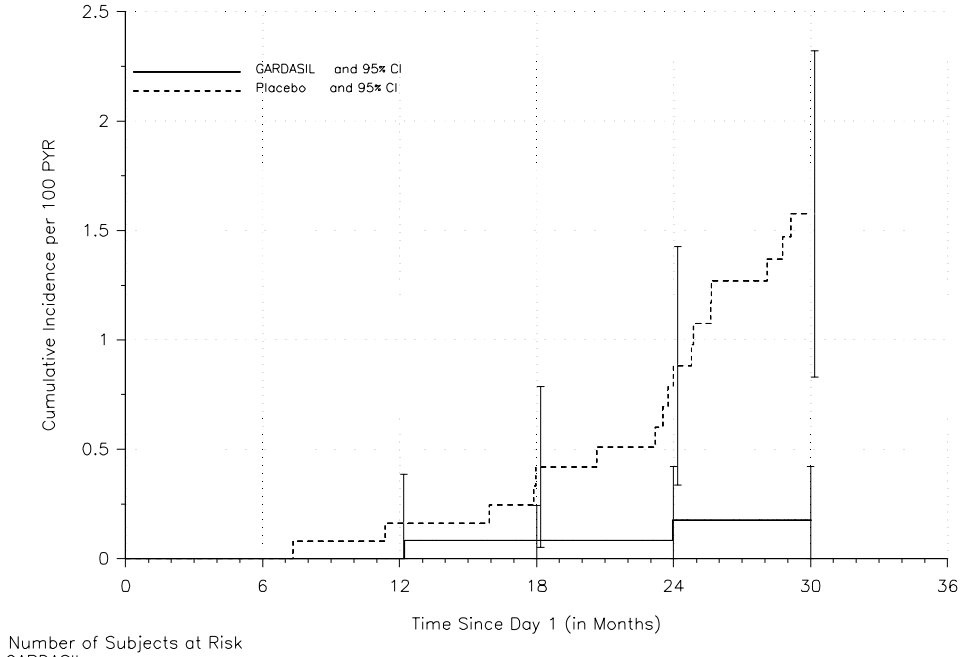
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects who have at least one follow-up visit after Month 7.

CI = Confidence interval; DNA = Deoxyribonucleic acid; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HPV = Human papillomavirus; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; PPE = Per-protocol efficacy.

Figure 4

Analysis of Time to HPV 6/11-Related Genital Warts
(Per-Protocol Efficacy Population) – Protocol 020



Number of Subjects at Risk

GARDASIL	1,245	1,245	1,223	1,140	1,058	904
Placebo	1,244	1,244	1,219	1,143	1,052	883

CI = Confidence interval; HPV = Human papillomavirus.

Table 7

Analysis of Efficacy of GARDASIL® in the FAS Population - (Protocol 020)

	GARDASIL® (N=2,025)				Placebo (N=2,030)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
HPV 6/11/16/18-Related EGL	1,943	27	4,625.7	0.6	1,937	77	4,556.5	1.7	65.5	(45.8, 78.6)
HPV 6/11-Related Condyloma acuminatum	1,943	24	4,635.4	0.5	1,937	71	4,558.8	1.6	66.8	(46.5, 80.0)
HPV 6/11/16/18-Related EGL By Lesion Type										
Condyloma acuminatum	1,943	24	4,635.4	0.5	1,937	72	4,558.8	1.6	67.2	(47.3, 80.3)
PIN 1 or worse	1,943	6	4,658.7	0.1	1,937	5	4,628.2	0.1	-19.2	(-393.8, 69.7)
PIN 1	1,943	3	4,666.1	0.1	1,937	4	4,629.7	0.1	25.6	(-339.9, 89.1)
PIN 2/3 or Cancer	1,943	3	4,663.1	0.1	1,937	2	4,628.6	0.0	-48.9	(-1682.6, 82.9)
PIN 2/3	1,943	3	4,663.1	0.1	1,937	2	4,628.6	0.0	-48.9	(-1682.6, 82.9)
Penile/Perianal/Perineal Cancer	1,943	0	4,670.6	0.0	1,937	0	4,630.5	0.0	NA	NA
HPV 6/11/16/18-Related EGL By HPV Type										
HPV 6-Related EGL	1,943	21	4,635.8	0.5	1,937	51	4,576.0	1.1	59.4	(31.2, 76.8)
HPV 11-Related EGL	1,943	6	4,663.7	0.1	1,937	25	4,606.6	0.5	76.3	(40.8, 92.0)
HPV 16-Related EGL	1,943	3	4,663.1	0.1	1,937	10	4,621.9	0.2	70.3	(-15.5, 94.7)
HPV 18-Related EGL	1,943	2	4,670.0	0.0	1,937	3	4,627.9	0.1	33.9	(-476.7, 94.5)
HPV 6/11/16/18-Related Persistent Infection By HPV Type	1,817	148	4,094.3	3.6	1,815	273	3,942.6	6.9	47.8	(36.0, 57.6)
HPV 6-Related Persistent Infection	1,817	63	4,213.8	1.5	1,815	112	4,139.4	2.7	44.7	(24.1, 60.1)

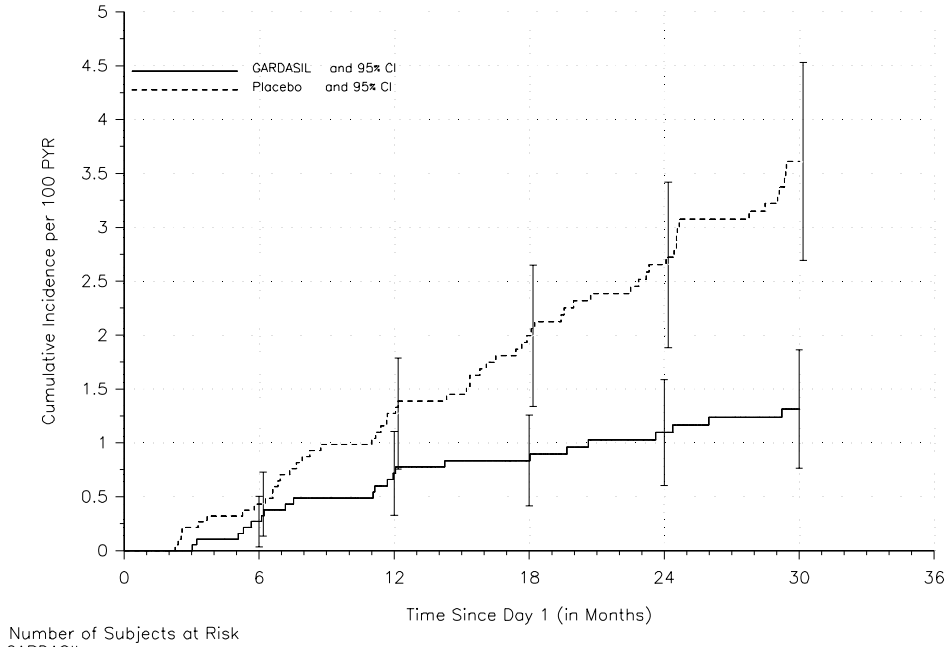
Analysis of Efficacy of GARDASIL® in the FAS Population - (Protocol 020) (Cont.)

	GARDASIL® (N=2,025)				Placebo (N=2,030)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
HPV 11-Related Persistent Infection	1,817	16	4,284.6	0.4	1,815	39	4,238.7	0.9	59.4	(25.7, 78.8)
HPV 16-Related Persistent Infection	1,817	71	4,199.5	1.7	1,815	131	4,112.7	3.2	46.9	(28.6, 60.8)
HPV 18-Related Persistent Infection	1,817	25	4,267.0	0.6	1,815	56	4,210.1	1.3	56.0	(28.2, 73.7)
HPV 6/11/16/18-Related DNA Detection	1,817	384	3,851.1	10.0	1,815	511	3,736.5	13.7	27.1	(16.6, 36.3)
By HPV Type										
HPV 6-Related DNA Detection	1,817	158	4,123.4	3.8	1,815	239	4,047.5	5.9	35.1	(20.3, 47.3)
HPV 11-Related DNA Detection	1,817	50	4,254.0	1.2	1,815	87	4,202.6	2.1	43.2	(18.7, 60.7)
HPV 16-Related DNA Detection	1,817	189	4,070.9	4.6	1,815	259	4,014.2	6.5	28.0	(12.9, 40.7)
HPV 18-Related DNA Detection	1,817	89	4,205.4	2.1	1,815	133	4,151.5	3.2	33.9	(13.0, 50.1)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one sub-category as he may have more than one lesion or multiple HPV types may be found in a lesion.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Day 1.
CI = Confidence interval; DNA = Deoxyribonucleic acid; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; FAS = Full analysis set; HPV = Human papillomavirus; PIN = Penile/Perianal/Perineal intraepithelial neoplasia.

Figure 5

Analysis of Time to HPV 6/11--Related Genital Warts
(Full Analysis Set) – Protocol 020



Number of Subjects at Risk

GARDASIL	1,943	1,835	1,715	1,581	1,424	1,185
Placebo	1,937	1,829	1,700	1,547	1,392	1,141

CI = Confidence interval; HPV = Human papillomavirus.

Table 8

Analysis of Efficacy Against EGL Due to any HPV Type
(Generally HPV Naïve Population and Full Analysis Set) – Protocol 020

	GARDASIL® (N=2,025)				Placebo (N=2,030)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
Generally HPV Naïve Population										
EGL Due to Any HPV Type	1,275	6	3,172.9	0.2	1,270	36	3,081.1	1.2	83.8	(61.2, 94.4)
HPV 6/11/16/18-Related EGL	1,275	3	3,174.5	0.1	1,270	31	3,086.9	1.0	90.6	(69.8, 98.2)
EGL Related to any of 10 Assay-identified HPV Types †	1,275	2	3,177.4	0.1	1,270	5	3,109.9	0.2	60.8	(-139.1, 96.3)
EGL Not Related to any of 14 Assay-identified HPV Types	1,275	2	3,165.5	0.1	1,270	5	3,071.6	0.2	61.2	(-137.0, 96.3)
Full Analysis Set Population										
EGL Due to Any HPV Type	1,943	36	4,612.6	0.8	1,937	89	4,538.6	2.0	60.2	(40.8, 73.8)
HPV 6/11/16/18-Related EGL	1,943	27	4,625.7	0.6	1,937	77	4,556.5	1.7	65.5	(45.8, 78.6)
EGL Related to any of 10 Assay-identified HPV Types	1,943	9	4,655.0	0.2	1,937	17	4,613.5	0.4	47.5	(-24.4, 79.4)
EGL Not Related to any of 14 Assay-identified HPV Types	1,943	6	4,562.4	0.1	1,937	12	4,477.9	0.3	50.9	(-41.3, 84.9)

† The 10 HPV types include HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.
Subjects are counted once in each applicable endpoint category. A subject may appear in more than one sub-category as he may have more than one lesion or multiple HPV types may be found in the lesions.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Day 1.
CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HPV = Human papillomavirus;
PIN = Penile/Perianal/Perineal intraepithelial neoplasia.

Table 9

Impact of GARDASIL® Vaccine on the Incidence of EGL Procedures
(Generally HPV-Naïve Population and Full Analysis Set) – Protocol 020

	GARDASIL® (N=2,025)				Placebo (N=2,030)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Incidence Reduction (%)	95% CI
Generally HPV Naïve Population										
EGL Biopsy	1,275	27	3,149.6	0.9	1,270	61	3,059.6	2.0	57.0	(31.3, 73.7)
EGL Therapy†	1,275	31	3,142.0	1.0	1,270	58	3,060.1	1.9	47.9	(18.1, 67.5)
Surgical	1,275	25	3,146.7	0.8	1,270	47	3,067.6	1.5	48.1	(14.0, 69.4)
Nonsurgical	1,275	7	3,172.8	0.2	1,270	14	3,104.0	0.5	51.1	(-29.5, 83.3)
Full Analysis Set Population										
EGL Biopsy	1,943	80	4,569.2	1.8	1,937	144	4,482.7	3.2	45.5	(27.9, 59.1)
EGL Therapy	1,943	90	4,550.1	2.0	1,937	142	4,478.5	3.2	37.6	(18.2, 52.6)
Surgical	1,943	70	4,578.1	1.5	1,937	120	4,505.0	2.7	42.6	(22.3, 57.9)
Nonsurgical	1,943	29	4,628.7	0.6	1,937	33	4,594.3	0.7	12.8	(-48.2, 48.9)

† Surgical therapy includes procedures such as surgical excision, laser ablation, cauterization, coagulation, and cryotherapy. Nonsurgical therapy includes topical treatments, including chemical ablation. Subjects are counted once in each applicable endpoint category. A subject may appear in more than one sub-category as more than one therapy may be applied.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Day 1.
CI = Confidence interval; EGL = External genital lesions; HPV = Human papillomavirus.

7.5 Impact of Baseline Characteristics on the Efficacy of GARDASIL®

Analyses of the efficacy of GARDASIL® against HPV 6/11/16/18-related EGL, persistent infection, and DNA detection in the PPE population, by categories of pre-specified covariates were conducted. Estimates of vaccine efficacy were generally comparable across all categories of: age at start of vaccination; race/ethnicity; geographic region; smoking status; circumcision status; condom usage; and lifetime number of sexual partners.

7.6 Duration of Efficacy

GARDASIL® vaccine efficacy has been shown for approximately 5 years post-dose 1 among young adult women. In men, Protocol 020 provides a shorter follow-up period (median duration of 2.9 years post-dose 1). A low incidence rate of HPV 6/11/16/18-related EGL observed among men in the vaccine group indicates sustained efficacy over this time period (Figure 4).

7.7 Efficacy Conclusions – Protocol 020

Based on the results of GARDASIL® efficacy analysis among PPE population, with supportive, consistent analyses results from the FAS population, the following conclusions can be made:

- Prophylactic administration of a 3-dose regimen of GARDASIL® to 16 to 26 year-old men is efficacious in preventing development of HPV 6/11-related external genital warts.
- Prophylactic administration of a 3-dose regimen of GARDASIL® to 16 to 26 year-old men is efficacious in preventing development of HPV 6/11/16/18-related persistent infection.
- Prophylactic administration of a 3-dose regimen of GARDASIL® to 16 to 26 year-old men is efficacious in preventing detection of HPV 6/11/16/18 DNA at one or more visits.

8. Immunobridging Results

This section presents data from analysis of comparison of immunogenicity between adolescent and adult males, and provides the basis for bridging efficacy from adult to adolescent males among whom a vaccine efficacy study is not feasible.

8.1 Results from Bridging Between Adult Men and Adolescent Boys

Table 10 displays GMTs at Month 7 and Month 24 among the adolescent and adult male populations receiving GARDASIL® and the results of the non-inferiority hypothesis test. At Month 7 and Month 24, antibody levels among male vacinees were robust in both age groups. At Month 7, adolescents had approximately 2- to 3-fold higher HPV type-specific antibody levels compared to adults. Non-inferiority of the Month 7 GMTs among adolescents relative to the adult males was established for all 4 HPV types contained in the vaccine.

Table 11 displays seroconversion rates at Month 7 and Month 24 among the adolescent and adult male populations receiving GARDASIL® and the results of the non-inferiority hypothesis test comparing rates at Month 7. One month after administration of dose 3, more than 97% of subjects in either age group seroconverted to the vaccine HPV-types. Non-inferiority of the Month 7 seroconversion rates among adolescents relative to the adult males was established for all 4 HPV types contained in the vaccine.

8.2 Parallel Testing of Sera from Adolescent and Adult Male Subjects

Since sera from Protocols 016 and 018 subjects were tested approximately 4 years prior to testing of Protocol 020 sera, a parallel testing procedure was undertaken in sera from a random sample of 490 vaccinated subjects (240 men from Protocol 020 and 250 boys from Protocols 016 and 018) to provide support for the immunobridging described in Section 8.1. The sample size was selected to ensure sufficient statistical power to address the immunobridging hypotheses. Results of this analysis indicated that anti-HPV responses (Month 7 GMTs and seroconversion rates) in the randomly selected 9 to 15 year-old boys were non-inferior to anti-HPV responses in the randomly selected 16 to 26 year-old men. Hence, non-inferiority of vaccine-induced anti-HPV response in adolescents compared to adult men was also demonstrated when samples were tested in parallel.

Table 10

Summary and Statistical Analysis of Anti-HPV Geometric Mean Titers Among Male Subjects Vaccinated with GARDASIL®
Comparing Boys to Adult Men
(Per-Protocol Immunogenicity Population)

Assay Study time	9 to 15 Year-olds[†] (N=1,073)			16 to 26 Year-olds[‡] (N=2,025)			Estimated Fold Difference Group A / Group B (95% CI)[§]	p-Value for Non-Inferiority[‖]
	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI		
Anti-HPV 6								
Month 07	885	1,036.9	(962.9, 1,116.6)	1,093	447.0	(418.2, 477.8)	2.32 (2.10, 2.56)	<0.001
Month 24	324	133.9	(119.3, 150.2)	906	80.3	(74.9, 86.0)		
Anti-HPV 11								
Month 07	886	1,386.3	(1,298.1, 1,480.4)	1,093	624.2	(588.4, 662.3)	2.22 (2.03, 2.43)	<0.001
Month 24	325	188.2	(168.1, 210.7)	906	94.5	(88.4, 101.2)		
Anti-HPV 16								
Month 07	883	6,047.1	(5,592.8, 6,538.3)	1,136	2,402.5	(2,242.6, 2,573.7)	2.52 (2.27, 2.79)	<0.001
Month 24	323	934.6	(822.0, 1,062.8)	937	347.8	(322.5, 375.1)		
Anti-HPV 18								
Month 07	888	1,356.9	(1,249.0, 1,474.2)	1,175	402.2	(374.3, 432.3)	3.37 (3.02, 3.76)	<0.001
Month 24	325	131.5	(111.7, 154.7)	966	38.7	(35.2, 42.5)		

[†] 9-15 year-old male subjects from Protocols 016 and 018. Month 24 testing was not included in Protocol 016
[‡] 16-26 year-old male subjects from Protocol 020
[§] Fold differences, confidence intervals and p-values are based on an ANOVA model with the term for age group.
[‖] For the null hypothesis that $GMT_{Boys}/GMT_{Men} \leq 0.5$ (2-fold decrease), a p-value <0.025 supports a conclusion that the specific type anti-HPV response in Boys is non-inferior to the response in Men.
N = Number of subjects randomized in the respective group who received at least 1 injection.
n = Number of subjects in the indicated immunogenicity population.
ANOVA = Analysis of variance; CI = Confidence interval; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units.

Table 11

Summary and Statistical Analysis of Anti-HPV Seroconversion Rates Among Male Subjects Vaccinated with GARDASIL®
Comparing Boys to Men
(Per-Protocol Immunogenicity Population)

Assay Study Time	9 to 15 Year-olds† (N=1,073)				16 to 26 Year-olds‡ (N=2,025)				Estimated Percentage Point Difference Group A - Group B§ (95% CI)	p-Value for Non-Inferiority §‖
		Seroconversion				Seroconversion				
	n	m	Percent	95% CI	n	m	Percent	95% CI		
HPV 6 cLIA ≥ 20 mMU/mL										
Month 7	885	884	99.9	(99.4%, 100%)	1,093	1,081	98.9	(98.1%, 99.4%)	1.0 (0.4, 1.8)	<0.001
Month 24	324	304	93.8	(90.6%, 96.2%)	906	823	90.8	(88.8%, 92.6%)		
HPV 11 cLIA ≥ 16 mMU/mL										
Month 7	886	885	99.9	(99.4%, 100%)	1,093	1,084	99.2	(98.4%, 99.6%)	0.7 (0.1, 1.5)	<0.001
Month 24	325	321	98.8	(96.9%, 99.7%)	906	866	95.6	(94.0%, 96.8%)		
HPV 16 cLIA ≥ 20 mMU/mL										
Month 7	883	881	99.8	(99.2%, 100%)	1,136	1,122	98.8	(97.9%, 99.3%)	1.0 (0.3, 1.9)	<0.001
Month 24	323	318	98.5	(96.4%, 99.5%)	937	930	99.3	(98.5%, 99.7%)		
HPV 18 cLIA ≥ 24 mMU/mL										
Month 7	888	886	99.8	(99.2%, 100%)	1,175	1,144	97.4	(96.3%, 98.2%)	2.4 (1.5, 3.5)	<0.001
Month 24	325	272	83.7	(79.2%, 87.5%)	966	602	62.3	(59.2%, 65.4%)		

† 9-15 year-old male subjects from Protocols 016 and 018. Month 24 testing was not included in Protocol 016
‡ 16-26 year-old male subjects from Protocol 020
§ Percentage differences, confidence intervals and p-values are based on the method of Miettinen and Nurminen. Confidence intervals for within –group percentages are based on exact methods.
‖ For the null hypothesis that $p_{Boys}/p_{Men} \leq -0.05$, a p-value <0.025 supports a conclusion that the specific type anti-HPV seroconversion rate in Boys is non-inferior to the seroconversion rate in Men.
Percent is calculated as 100*(m/n).
N = Number of subjects randomized in the respective group who received at least 1 injection.
n = Number of subjects in the indicated immunogenicity population.
m = Number of subjects with the indicated response.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units.

8.3 Conclusions Regarding the Immunogenicity of GARDASIL®

Overall, the following conclusions can be made based on the immunogenicity findings of the studies of GARDASIL® in males:

- Prophylactic administration of a 3-dose regimen of GARDASIL® to 16 to 26 year-old men generates robust anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses that result in a high level of protective efficacy through 2.9 years after onset of the vaccination regimen.
- Vaccine-induced anti-HPV levels in 9-15 year-old boys are non-inferior to anti-HPV levels in 16-26 year-old men, inferring vaccine efficacy in this younger age group as well.

9. Clinical Safety Results

In this section safety data on GARDASIL® when administered to males 9 to 26 years of age are detailed. Data indicate that GARDASIL® is generally well tolerated in this population, and the safety profile is consistent with what has been observed in other populations, as described in Section 10.

9.1 Serious Adverse Experiences (SAEs), Deaths, and Discontinuations

Table 12 presents the overall summary of adverse experiences (Days 1 through 15 following any vaccination visit) in male subjects in Protocols 016, 018, and 020. Within 15 days following any vaccination visit, a larger number of subjects in the group that received GARDASIL® experienced a serious adverse experience compared with the placebo group, although the numbers were small. There were no serious adverse experiences determined by the clinical investigator to be vaccine-related. In the vaccine group, 9 subjects experienced 11 serious adverse experiences including intentional overdose (non-study medication), acute renal failure, localized infection and pain in extremity (same subject), type I diabetes mellitus, appendicitis, non-cardiac chest pain, cellulitis, convulsion and varicella (same subject), and hypersensitivity (due to peanuts). In the placebo group, 1 subject experienced a serious adverse experience of contusion. There were no deaths in Days 1 to 15 following any vaccination period. Discontinuations due to an adverse experience were rare; and the proportions of subjects who discontinued the study due to an adverse experience were comparable between the vaccination groups (0.2% of subjects in both vaccine and placebo groups).

During the entire follow-up period in the studies, (including the period beyond 1-15 days following vaccination), there were an additional 24 male subjects with serious adverse experience (13 were in the vaccine group, 11 in the placebo group). None were considered as vaccine-related by the investigators.

Table 13 presents the listing of serious clinical adverse experiences reported at any time during the course of the clinical studies. The vaccination groups were comparable with respect to the types of serious adverse experiences reported.

Table 14 presents the number of subjects who experienced clinical adverse experiences resulting in death. Overall, 14 male subjects died at any time during Protocols 016, 018 and 020. All deaths reported in male subjects occurred more than 15 days following

vaccination, and none of the deaths in either vaccination group were determined by the investigator to be vaccine/placebo- or procedure-related. No deaths were reported during the study in Protocol 018. One male subject, who was enrolled in Protocol 018 and received placebo died due to medulloblastoma after completing the study (and is therefore not included in the clinical database).

Of the 14 subjects who died at any time during the clinical studies, 4 were in the GARDASIL® group and 10 were in the placebo group. In the group that received GARDASIL®, the 4 subjects who died had the following adverse experiences; arrhythmia, road traffic accident/cervical vertebral fracture (same subject), gun shot wound/traumatic intracranial hemorrhage (same subject), and traumatic brain injury/cardiac arrest (same subject). In the group that received placebo, 10 subjects who died had the following adverse experiences; accidental overdose, gun shot wound/pericardial hemorrhage (same subject), gun shot wound, gun shot wound/head injury (same subject), completed suicide (2 subjects), multiple drug overdose, road traffic accident, myocardial ischemia, and chemical poisoning.

One subject in Protocol 020 enrolled more than once and was excluded from Table 12. This subject was considered as serious adverse experience due to the overdose in Day 1 to 15 following a vaccination; the subject received a total of 4 doses of placebo and 2 doses of GARDASIL®.

Two (2) additional subjects in P020 enrolled more than once and had serious adverse experiences of overdose after Day 15 following a vaccination. These subjects were also excluded from the safety tables. One subject received a total of 6 doses of placebo and the second subject received a total of 3 doses of GARDASIL® and one dose of placebo. No additional adverse experiences were reported from these subjects.

Table 12

Summary of Adverse Experiences, Serious Adverse Experiences, Deaths, and Discontinuations Among Male Subjects 9-26 Years of Age - Protocols 016, 018, and 020 (Days 1 to 15 Following any Vaccination)

	GARDASIL® † (N=3,092)		Placebo † (N=2,303)	
	n	(%)	n	(%)
Subjects with follow-up	3,002		2,219	
Number (%) of subjects:				
With one or more adverse experiences	2,216	(73.8)	1,417	(63.9)
With injection site adverse experiences	1,927	(64.2)	1,177	(53.0)
With systemic adverse experiences	1,118	(37.2)	7,23	(32.6)
With serious AEs ‡	9	(0.3)	1	(0.0)
With serious vaccine-related AEs	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to an AE ‖	6	(0.2)	4	(0.2)
Discontinued due to a vaccine-related AE	4	(0.1)	3	(0.1)
Discontinued due to a serious AE	1	(0.0)	0	(0.0)
Discontinued due to a serious vaccine-related AE	0	(0.0)	0	(0.0)

† There were a total of 7 subjects who received a mixed vaccine/placebo regimen that are not counted in the safety tables. One subject from P018 and 6 subjects from P020. As all male subjects in Protocol 016 were vaccinated, the number of subjects who received GARDASIL® is higher than those received placebo.

‡ One subject in P020 was excluded from this table as he enrolled more than once. The subject had a serious AE of overdose in Day 1 to 15 following a vaccination. See section 9.1 for details.

‖ Discontinued – Subject discontinued from therapy

AE = Adverse Experience

Table 13

Listing of Serious Clinical Adverse Experiences Among
Male Subjects 9-26 Years of Age
- Protocols 016, 018, and 020
(Entire Study Period)

	GARDASIL®	Placebo
Total Number of Serious Clinical Adverse Experiences †	20	13
Abdominal Pain	1	0
Accidental Overdose	0	1
Appendicitis	1	0
Arrhythmia	1	0
Cardiac Arrest	1	0
Cellulitis	1	0
Cervical Vertebral Fracture	1	0
Chemical Poisoning	0	1
Contusion	0	1
Completed Suicide	0	2
Convulsion	1	0
Diarrhea	1	0
Hypersensitivity	1	0
Gun Shot Wound	1	3
Head Injury	0	1
Localized Infection	1	0
Multiple Drug Overdose	0	1
Myocardial Ischemia	0	1
Non Cardiac Chest Pain	1	0
Pain in Extremities	1	0
Pericardial Hemorrhage	0	1
Renal Failure	1	0
Road Traffic Accident	1	1
Traumatic Brain Injury	1	0
Traumatic Intracranial Hemorrhage	1	0
Type 1 Diabetes Mellitus	1	0
Varicella	1	0
Vomiting	1	0

† Three subjects in P020 were excluded from this table as they enrolled more than once. Each subject had a serious AE of overdose. See section 9.1 for details.

Table 14

Listing of Clinical Adverse Experiences Resulting in Death Among
Male Subjects 9-26 Years of Age - Protocols 016, 018, and 020
(Entire Study Period)

	GARDASIL®	Placebo
Total Number of Deaths†	4	10
Accidental Overdose	0	1
Arrhythmia	1	0
Chemical Poisoning	0	1
Completed Suicide	0	2
Gun Shot Wound	0	1
Gun Shot Wound/Pericardial Hemorrhage	0	1
Gun Shot Wound/Head Injury	0	1
Gun Shot Wound/Traumatic Intracranial Hemorrhage	1	0
Multiple Drug Overdose	0	1
Myocardial Ischemia	0	1
Road Traffic Accident	0	1
Road Traffic Accident/ Cervical Vertebral fracture	1	0
Traumatic Brain Injury/Cardiac Arrest	1	0

† None of the deaths was considered to be vaccine-related by the investigators.

9.2 Injection-Site Adverse Experiences

Among the three clinical trials of GARDASIL® in boys and men, two different types of placebo were used. These were the non-aluminum containing placebo used in Protocol 018 and the aluminum-containing placebo used in Protocol 020 (in Protocol 016 all boys received GARDASIL®). Injection site adverse experiences were summarized for GARDASIL® and each of the placebo types administered.

The proportion of subjects who reported at least one injection-site adverse experience within 5 days after any vaccination was 64.1% among subjects who received GARDASIL® and 53.6% among subjects who received aluminum-containing placebo. Most injection-site adverse experiences were judged by the study subjects to be mild or moderate in intensity. In the GARDASIL® group 2.0% of subjects and in the aluminum-containing placebo group 1.0% of subjects reported injection site adverse experience of severe intensity. The most common injection-site adverse experiences reported were pain, swelling, and erythema.

Among recipients of non-aluminum containing placebo, 47.6% reported at least one injection site adverse experience and 0.7% of such placebo recipients reported a maximum intensity of severe.

These data indicate that a higher proportion of subjects in the GARDASIL® group reported injection site adverse experiences compared to either group of placebo recipients; the difference was bigger when compared to non-aluminum containing placebo group. Overall, a small proportion of subjects reported maximum intensity of severe for injection site adverse experiences in any of the groups.

9.3 Systemic Adverse Experiences

The proportion of subjects who reported a systemic clinical adverse experience occurring Days 1 to 15 following any vaccination was slightly higher in the GARDASIL® group (37.2%) compared to placebo group (32.6%) (Table 12). The great majority of these adverse experiences were judged to be mild or moderate in intensity. The proportions of subjects who reported a severe intensity systemic adverse experience were comparable between the vaccination groups (4.3% in GARDASIL® group versus 3.0% in placebo group). The most common systemic adverse experiences were headache and pyrexia. In the GARDASIL® group 12.3% and 8.2% of subjects reported headache and pyrexia, respectively. In the placebo group, headache was reported by 11.2% and pyrexia was reported by 6.5% of subjects.

9.4 Elevated Temperatures

Elevated temperature (fever) was defined as a temperature (≥100˚F [≥37.8˚C], oral or oral equivalent) within 5 days following any vaccination. Most subjects had a maximum temperature <100˚F (<37.8˚C) oral or oral equivalent. The proportions of subjects who reported an elevated temperature or who reported a maximum temperature ≥39.9˚C were small and were comparable between the vaccination groups. In the GARDASIL® group 0.3% of subjects had temperatures of ≥103.8˚F (≥39.9˚C) and in the placebo group 0.1% of subjects had temperatures ≥103.8˚F (≥39.9˚C).

9.5 New Medical Conditions

Overall, 46.1% of male subjects who received GARDASIL® in Protocols 016, 018, and 020 reported one or more new onset medical conditions after Day 1, compared to 42.0% of male subjects who received placebo in these studies. In the group that received GARDASIL®, the most common new medical conditions reported include infections (pharyngitis, upper respiratory tract infection, and nasopharyngitis). In the placebo group, the most common medical conditions reported also include infections (upper respiratory tract infection, pharyngitis, and fungal skin infection).

Overall 1.3% of subjects in both GARDASIL® and placebo groups among male subjects in Protocols 016, 018 and 020 reported a new medical condition that could potentially be indicative of an autoimmune phenomenon. In both groups, the most common new medical condition potentially indicative of an autoimmune phenomenon was arthralgia (1.0% in the group that received GARDASIL® and 0.7% in the placebo group), followed by vitiligo (0.1% in the group that received GARDASIL® and 0.2% in the placebo group). No cases of Guillain Barre Syndrome or multiple sclerosis were reported in these clinical studies. No trends or patterns of new medical conditions to suggest safety signals were noted.

9.6 Conclusions Regarding the Safety of GARDASIL®

The safety data presented in this supplemental Application support the conclusion that GARDASIL® is generally well tolerated and displays a favorable safety profile similar to that shown (Section 10) in women. Specifically, the following conclusions can be drawn:

- Administration of GARDASIL® is generally well-tolerated in 9 to 26 year-old boys and men.
- Boys and men 9 to 26 years of age who begin the 3-dose regimen of GARDASIL® rarely discontinue vaccination due to a clinical adverse experience.

Overall, the safety profile observed in boys and men 9 to 26 years of age in Protocols 016, 018, and 020 is favorable and consistent with the safety profile observed in clinical studies in girls and women 9 to 26 years of age. In addition, the safety profile is consistent with current approved product circular.

10. Overall Safety Data on GARDASIL®

In order to provide perspective on the safety of GARDASIL® demonstrated in males, the following summary of overall safety of GARDASIL® in women, including both data from clinical trials and the post-marketing environment, is provided.

10.1 Clinical Trial Data in 9 to 45 Year-Old Females

Overall, 12,614 female subjects aged 9-45 years received at least 1 dose of GARDASIL® in one of 6 protocols using the quadrivalent vaccine (Protocols 007, 013, 015, 016, 018 and 019).

Table 15 presents the overall summary of adverse experiences Day 1 to 15 following any vaccination, and Table 16 presents all deaths reported during the entire study period (Day 1 through last study visit).

A larger proportion of subjects who received GARDASIL® reported an adverse experience compared with placebo subjects. This finding was caused by an increase in the proportion of subjects in the group that received GARDASIL® who reported an injection-site adverse experience compared with the placebo group. Four serious adverse experiences reported Days 1 to 15 postvaccination in the GARDASIL® group were considered vaccine-related by the investigators. These serious adverse experiences were bronchospasm, gastroenteritis, headache/hypertension (same subject), injection site joint movement impairment/injection site pain (same subject). None of the deaths reported in clinical trials of GARDASIL® in females were considered as vaccine-related by the investigators. Two of the deaths occurred within Days 1 to 15 and these were overdose/convulsion (same subject, cocaine overdose) and traffic accident/cardiac arrest/multiple injuries (same subject).

In summary:

- serious adverse experiences occurred infrequently;
- the proportions of subjects who experienced a serious adverse experience were similar between the vaccination groups;

- serious adverse experiences determined by the clinical investigator to be vaccine-related were infrequent;
- the proportions of subjects who experienced a serious adverse experience determined by the clinical investigator to be vaccine-related were similar between the vaccination groups;
- discontinuations due to an adverse experience were infrequent ; and
- the proportions of subjects who discontinued the study due to an adverse experience were similar between the vaccination groups.

Table 15

Summary of Adverse Experiences, Serious Adverse Experiences, Deaths, and Discontinuations Among Female Subjects 9-45 Years of Age
Safety Population - Protocols 007, 013, 015, 016, 018, and 019
(Days 1 to 15 Following any Vaccination)

	GARDASIL® † (N=12,614)		Placebo † (N=11,314)	
	n	(%)	n	(%)
Subjects with follow-up	12,472		11,195	
Number (%) of subjects:				
With one or more adverse experiences	6,493	(47.9)	5,012	(44.8)
With injection site adverse experiences	5,880	(47.1)	4,122	(36.8)
With systemic adverse experiences	4,352	(34.9)	3,585	(32.0)
With serious AEs	52	(0.4)	49	(0.4)
With serious vaccine-related AEs †	4	(0.0)	2	(0.0)
Who died	2	(0.0)	1	(0.0)
Discontinued due to an AE ‖	15	(0.1)	11	(0.1)
Discontinued due to a vaccine-related AE	11	(0.1)	6	(0.1)
Discontinued due to a serious AE	2	(0.0)	3	(0.0)
Discontinued due to a serious vaccine-related AE	0	(0.0)	1	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine
‖ Discontinued – Subject discontinued from therapy
Percentages are calculated based on the number of subjects with follow-up
AE = Adverse Experience
N=Number of subjects who received at least one dose of GARDASIL® or placebo.

Table 16

Listing of Clinical Adverse Experiences Resulting in Death Among Female Subjects 9-45 Years of Age - Protocols 007, 013, 015, 16, 018, and 019 (Entire Study Period)

	GARDASIL®	Placebo
Total Number of Deaths	14	8
Adenomyosis/Dehydration/Endometriosis/Renal Failure Acute/Upper GI hemorrhage/Uterine Leiomyoma/Pulmonary Embolism/Acute Respiratory Failure	1	0
Asphyxia	0	1
Completed Suicide	1	1
Completed Suicide/Intentional Overdose	0	1
Deep Vein Thrombosis/Pulmonary Embolism	1	0
Deep Vein Thrombosis/Pulmonary Embolism/Acute Respiratory Distress Syndrome/Renal Failure	0	1
Head Injury	1	0
Hyperthyroidism/Cardiac Failure/Cardio-respiratory Arrest	1	0
Infective Thrombosis/Myocarditis/Septic Shock	1	0
Overdose†/Convulsion	1	0
Pancreatic Carcinoma	1	0
Pneumonia/Sepsis	1	0
Pneumonia/Acute Lymphatic Leukemia/Acute Respiratory Failure/Pharyngitis/Pulmonary Embolism	0	1
Pulmonary Tuberculosis	1	0
Road Traffic Accident	1	2
Road Traffic Accident/Injury	0	1
Road Traffic Accident/Cardiac Arrest/Multiple injuries	1	0
Road Traffic Accident/Thermal Burn	1	0
Systematic Lupus Erythematosus/Pericarditis	1	0

† Cocaine overdose.

10.2 Summary of Post-marketing Data

Merck has continued monitoring safety profile of GARDASIL® since its licensure, including conducting postmarketing safety surveillance (Section 10.2.1) and a postlicensure safety study (Section 10.2.2). In addition, the United States Centers for Disease Control and Prevention (CDC) conducts surveillance for safety of vaccines including GARDASIL® (Section 10.2.3).

10.2.1 Post-marketing Safety Surveillance

From the International Birthdate (i.e. the date of first regulatory approval worldwide, 1-June-2006) through 31-May-2009, over 50 million doses of GARDASIL® were distributed worldwide; there were no countries where marketing applications have been rejected, withdrawn, suspended, or revoked for safety reasons. The sixth 6 month Periodic Safety Update Report (PSUR) covering the time period of 01-Dec-2008 thru 31-May-2009 contains a list of 104 countries where GARDASIL® has received marketing approval up to 31-May-2009.

To permit safety surveillance for its products, Merck & Co., Inc. maintains the New Worldwide Adverse Experience System (NWAES) database. Postmarketing safety surveillance is a worldwide, passive, spontaneous, and voluntary reporting system. At Merck & Co. Inc., the NWAES database contains all spontaneous adverse experience reports from the marketed environment, serious reports from clinical trials, and reports from the medical literature. This is a dynamic database, and adverse experience information is updated continuously. The retrieval of data is provided as a snapshot in time. The data are compiled and reviewed on a periodic basis and reported in a PSUR.

All of the reports are entered into NWAES and are coded using the terminology of the reporter. The Medical Dictionary for Regulatory Activities (MedDRA) is the dictionary used to code adverse experience terms in the NWAES database. Inclusion of the report in the database implies only a temporal association and not necessarily a causal association. Each report represents one individual who may experience one or more adverse experiences. Since each adverse experience is coded to a body system, one report may contain multiple adverse experiences in the same or different body systems.

Routine Pharmacovigilance practices include continuous monitoring of the safety profile of approved products. Data from the NWAES database are routinely reviewed as individual reports and in aggregate. The purpose of the review is to evaluate adverse experience reports for possible safety signals, to determine if further investigation is warranted to clarify the safety profile of the product, and to ensure completeness of safety information in worldwide package circulars. This approach is in line with generally accepted pharmacovigilance approaches including the European Union requirements.

A query of the NWAES database performed on 14-Jun-2009 revealed that 30,231 spontaneous reports have been received from product launch through 31-May-2009; 3,487 reports (12%) were considered serious. The 5 most frequently reported adverse experiences included no adverse event (6632), inappropriate schedule of drug administration (5756), drug exposure during pregnancy (2735), syncope (2478), and

dizziness (2273). The events of syncope and dizziness are listed in the United States product label. The term "no adverse event" is coded when another event, such as a medication error term such as "overdose" is coded. It is important to note whether or not an adverse event was associated with these medication errors.

There have been reports of males being vaccinated with this product but there is no way to estimate the number who have been vaccinated. As of 14-Jun-2009, 198 spontaneous reports involving male patients have been received in the NWAES database from product launch through 31-May-2009 (these were included in the total of 30,231); 6 reports (3%) were considered serious. The 5 most frequently reported adverse experiences which involved male patients included off label use (93), no adverse event (93), wrong drug administered (34), inappropriate schedule of drug administration (25), and accidental exposure (17). The 6 serious reports included 6 serious adverse experiences as follows: convulsion (2), Guillain Barre Syndrome (1), tendon rupture [secondary to trauma] (1), diarrhea (1), and inappropriate schedule of drug administration (1). Note that this latter report of inappropriate schedule of drug administration involved a 1 month old male who was inadvertently exposed to GARDASIL® and was hospitalized for observation; there was no adverse event experienced.

Overall, the post licensure experience with GARDASIL® collected through passive reporting of spontaneous adverse experiences to Merck & Co., Inc. has confirmed the favorable safety profile of the vaccine, with a low proportion of reported serious adverse experiences; the benefit-risk profile for the product remains favorable. Because the product has not been widely used in male patients the data from the post marketing environment is insufficient to draw conclusions regarding the safety profile of the vaccine relative to males. To date, however, the type of adverse experiences spontaneously reported in males do not suggest a unique safety concern for that gender.

Merck & Co., Inc will continue to monitor the safety of GARDASIL® in the post-licensure period.

10.2.2 Post-Licensure Safety Study

The GARDASIL® Post-Licensure Surveillance Program (i.e. the "GARDASIL® Safety Study") is being conducted at two large managed care organizations, Kaiser Permanente Northern California and Kaiser Permanente Southern California. An independent, external Safety Review Committee (SRC) reviews the study's surveillance data for evidence of any safety signals associated with GARDASIL®. To date, no safety signals associated with GARDASIL® vaccination were detected for pre-specified autoimmune conditions or for death in a base population of 142,547 females who received ≥1 dose of GARDASIL®. No safety signals were identified in this same base population with respect to adverse pregnancy outcomes. Additionally, with the exception of syncope and possibly cellulitis, no safety signals were detected for emergency room visits and hospitalizations evaluated among 22,527 females who received 3 doses of GARDASIL® per protocol (i.e. 9-26 years old at first dose; Kaiser member at each dose; minimum of 28 days between doses 1 and 2, and 12 weeks between doses 2 and 3). Of 3 confirmed syncope cases on Day 0 (the day of vaccination) in the emergency room setting, two were temporally associated with vaccination. Also, 2-3 potential cases of cellulitis occurring

in the emergency room/hospital setting on post-vaccine Days 2-10 were possibly associated with GARDASIL® vaccination, though other concomitant vaccines were administered in each case. The SRC noted that some cellulitis cases may have been injection site reactions rather than acute infection. Limited information in available medical charts impeded further assessment of these cases. In summary, the data obtained to date from the GARDASIL® Safety Study indicate a safety profile consistent with what has been reported from other sources previously. The study is ongoing.

10.2.3 CDC Review of Safety Surveillance Data

The CDC reviewed post-licensure safety data from 3 different CDC safety surveillance projects at the October, 2008 Advisory Committee on Immunization Practices (ACIP) meeting [7; 8; 9].

The outcomes reviewed from the Vaccine Adverse Events Reporting System (VAERS), a national passive surveillance system of adverse events in the United States, included general data as well as several selected serious conditions of clinical interest (syncope, venous thromboembolism, Guillain-Barre Syndrome, transverse myelitis and deaths). The CDC noted that reporting to VAERS has been robust since vaccine licensure, likely the result of vaccine publicity and a general increase in adverse event reporting. However, the majority of the reports were non-serious (94%) and consistent with pre-licensure trial data. It was specifically noted that the reported cases of venous thromboembolism were associated with predisposing factors, such as hormonal contraceptive use, co-morbidities and life-style risks. The review of the reported deaths revealed that there was no clustering by age groups, onset intervals or dose number. In addition, there were no trends in clinical conditions which preceded or cause death.

The Vaccine Safety Datalink (VSD) is a collaboration between the CDC and 8 managed care organizations (8.8 million members or 3% of United States population). It was established in 1990 designed to improve vaccine safety through active surveillance and epidemiological studies. Several selected conditions were evaluated in the VSD and reported at the October, 2008 ACIP meeting – Guillain Barre Syndrome, seizures, syncope, appendicitis, stroke, venous thromboembolism, anaphylaxis and other allergic reactions. The CDC concluded that the VSD active surveillance did not find statistically significant risk for any of these pre-specified adverse events after vaccination.

The CDC also summarized a review of the Clinical Immunization Safety Assessment (CISA) Network, a network of six academic centers with safety subject matter experts, established in 2001 to investigate the pathophysiologic mechanisms and biologic basis of adverse events following immunizations. CISA centers reviewed reports of transverse myelitis and Guillain Barre Syndrome from VAERS, and concluded that the scientific evidence was insufficient to support a causal relationship between GARDASIL® and these selected adverse events.

In summary, the data reviewed and presented by the CDC summarized experience of 20 million doses under passive surveillance and > 375,000 doses under active surveillance and affirmed the positive benefit-risk profile of vaccination with GARDASIL®.

10.3 Overall Safety Conclusion

Clinical trial safety data, passive post-marketing safety surveillance and active, controlled evaluations of selected conditions of clinical interest all confirm the overall positive safety profile of GARDASIL®.

11. Benefits and Risk Conclusions

In the prior Applications for GARDASIL®, the vaccine was shown to be efficacious, immunogenic, and generally well-tolerated in girls and women 9 to 26 years of age. In addition, the vaccine was shown to be immunogenic and generally well-tolerated in boys 9 to 15 years of age. In this Application, efficacy, immunogenicity and safety of GARDASIL® in men 16 to 26 years of age have been demonstrated. In addition, efficacy among adult men was successfully bridged to adolescent boys 9 to 15 years of age based on immunogenicity. Therefore, the benefit-risk profile is favorable and the totality of the data supports broadening the GARDASIL® indication to males 9 to 26 years of age.

11.1 Unmet Medical Need for HPV Vaccination in Men

As demonstrated in Protocol 020 and in published studies of HPV infections in men, anogenital HPV-related infection and diseases are common and associated with significant individual and public health burden. HPV types contained in the vaccine constitute a substantial proportion of these diseases and infection and a vaccine highly efficacious in preventing such diseases and infection would provide significant benefit for the individual and public health in general.

HPV is one of the most common STIs, and HPV types contained in GARDASIL® constitute a substantial proportion of these infections in men. Consistent with previous published literature, in Protocol 020 approximately 9% of HM subjects had evidence of prevalent infection with at least one of the 4 vaccine HPV types. This prevalence is probably higher in the general population, as the study restricted enrollment to those with limited number of sexual partners. Furthermore, similar to findings in women, persistent infections were found to significantly predict development of clinical disease in men. Therefore, a vaccine that prevents persistent infection with HPV would also prevent the disease that may occur subsequent to such infections.

There is no clinically proven method to protect against anogenital HPV infections and diseases. Although circumcision and condom use have been suggested to be associated with reduced rates of infection, they do not provide complete protection. Analysis of data from placebo subjects in Protocol 020 showed that neither affords full protective effect against prevalent or incident HPV infection. Thus, vaccination is the optimal method of HPV prevention.

Genital warts are the most common manifestation of HPV infection in men, and young adult men are at the highest risk for developing HPV-related anogenital diseases. Based on Protocol 020, in a general population of young HM, 1.5 out of 100 develops genital warts every year. Extrapolating this incidence rate to the United States male population data suggests that approximately 350,000 new cases of genital warts occur every year among men 16-26 years of age. This incidence rate is higher than what has been reported in the literature for genital warts in the same age range, and signifies that burden of

disease due to anogenital warts has been underestimated. Furthermore, these rates are substantially higher in high-risk populations, such as MSM. However, this incidence rate from Protocol 020 may still underestimate the true incidence of genital warts, because men with greater than 5 sexual partners before enrollment were excluded.

The incidence of anogenital warts has been increasing significantly in recent years. This finding is corroborated by several sources in different countries. Warts-related direct health care costs are conservative as they do not include health care visits that take place outside the systems analyzed (i.e. health care providers of privately insured patients) and indirect costs associated with warts. Patients experience discomfort, pruritus, psychosocial burden, and stigmatization, and require multiple health care visits. A myriad of treatment methods, from topical to surgical, are not optimal in that they carry risks to varying degree for scarring, disfigurement, pain, and relapse.

Infection with high-risk HPV can also cause penile and anal cancers in men. As high as 90% of anal cancer and 40-50% of penile cancer are due to HPV; HPV 16/18, which are contained in the GARDASIL®, constitute most of the causal HPV type. As demonstrated in women, these HPV-related cancers are also preceded by high-grade intraepithelial neoplasia (i.e. in men PIN 2/3 and AIN 2/3).

In summary, there is a strong public health rationale for immunization of men against HPV. A vaccine to reduce the burden of HPV-related anogenital diseases in men would have significant individual and public health benefit.

11.2 New Information Presented in the Current Application and Benefits of GARDASIL® Vaccination of Boys and Men 9-26 Years of Age

As demonstrated in Protocol 020, administration of GARDASIL® to 16 to 26 year-old men is highly efficacious in preventing HPV 6/11/16/18-related external genital lesions (external genital warts and penile/perianal/perineal intraepithelial neoplasia) GARDASIL® reduced the incidence of HPV 6/11/16/18-related external genital lesions by 90.4% (95% CI: 69.2, 98.1). Efficacy was high against HPV 6/11-related genital warts [89.3% (95% CI: 65.5, 97.9)], the lesion most commonly detected in the study. These data confirm the benefit that the vaccine provides in preventing HPV 6- and/or 11-related genital warts in young men.

Data from Protocol 020 also demonstrated that there is significant reduction in overall burden of HPV-related external genital diseases through vaccination with GARDASIL®. This impact was consistently observed regardless of subpopulation examined, young men who are HPV-naïve or a general population of young men (including those who are HPV-naïve or infected) and across geographic regions. Analysis showed that efficacy of GARDASIL® emerges soon after the vaccination series is completed.

As presented in previously published studies, treatment modalities for genital warts can be costly and are an important public health burden. Vaccine efficacy against external genital therapies was 47.9% (95% CI: 18.1, 67.5) in the GHN and 37.6% (95% CI: 18.2, 52.6) in the FAS populations. As demonstrated in Protocol 020, GARDASIL® significantly reduces therapies related to external genital lesions.

GARDASIL® is also efficacious against HPV 6/11/16/18-related persistent infection and DNA detection at one or more visits. Persistent infection with HPV 6/11/16/18 significantly predicts development of external genital lesions; the high rate of reduction in persistent infection through vaccination is a major benefit and highly relevant to our understanding of how the vaccine prevents disease. GARDASIL® also reduced HPV 6/11/16/18 DNA detection of any duration nearly by 45%.

Immunogenicity data from Protocol 020 showed that GARDASIL® was highly immunogenic in men 16-26 years of age. Vaccine-induced anti-HPV levels in 9-15 year-old boys were non-inferior to anti-HPV levels observed in 16-26 year-old men, inferring vaccine efficacy in this younger group as well. As GARDASIL® is preventative, targeting adolescents prior to sexual debut and HPV exposure is critical.

Administration of GARDASIL® was shown to be generally well-tolerated in all populations in which it was evaluated. The proportions of subjects who reported serious adverse experiences, or who discontinued due to an adverse experience were low and comparable between vaccination groups. Injection-site adverse experiences were more common among subjects who received GARDASIL® compared with placebo subjects, but most of these adverse experiences were mild or moderate in intensity. Overall, the proportions of subjects who reported new medical conditions, including conditions potentially indicative of an autoimmune phenomenon, were comparable between vaccination groups.

In summary, GARDASIL® is efficacious, immunogenic, and generally well-tolerated when administered to males 9 to 26 years of age.

11.3 Modeling the Public Health Impact of HPV Vaccination

A population impact analysis was conducted with the purpose of projecting the health impact of extending the current GARDASIL® recommendation for girls and women in the United States to boys and men. In brief, a previously developed mathematical model was extended and updated to evaluate the impact of a GARDASIL® vaccination program in female and male persons 9 to 26 years of age in the United States. This analysis extended the previous model by incorporating the most current vaccine efficacy results from the GARDASIL® clinical trials in males and females (Protocols 007, 012, 020). In addition to a direct benefit to men, the model also evaluated if male GARDASIL® vaccination could provide benefit to women through potentially impacting disease transmission. The analysis found that broadening the current GARDASIL® recommendation for girls and women 9 to 26 years of age to boys and men 9 to 26 years of age would further decrease the cumulative number of genital wart cases, CIN cases, cervical cancer cases, and cervical cancer deaths in the United States by 1,900,000, 270,000, 5000, and 1000, respectively, within 50 years following the introduction of the vaccine.

In summary, the results from this model suggest that in a setting of organized cervical cancer screening, a prophylactic GARDASIL® can reduce genital warts, CIN, cervical cancer, and cervical cancer deaths when implemented as a strategy that combines vaccination of both females and males 9 to 26 years of age compared to only vaccinating females 9 to 26 years of age.

12. Overall Summary and Conclusions

The data contained in the current supplemental Application strongly support the main conclusions of the prior Applications. There is strong evidence for efficacy in the study group that is representative of the population for which GARDASIL® is intended, with a favorable safety profile. There is substantial vaccine preventable HPV infection and disease in boys and men. Administration of GARDASIL® to male adolescents and adults is highly likely to induce protection through periods of high risk for acquisition of infection and disease with the vaccine HPV types. GARDASIL® therefore addresses an important unmet medical need and will significantly reduce the public health burden caused by the HPV types contained in the vaccine. Thus, the overall benefit-risk profile in boys and men is favorable, and on the basis of the data presented in the current supplemental Application and the prior Applications, the indication in boys and men proposed below is justified:

GARDASIL® is indicated in boys and men 9 through 26 years of age for the prevention of genital warts (condyloma acuminata) caused by HPV types 6 and 11.

13. List of References

1. Southern SA, Herrington CS. Molecular events in uterine cervical cancer. Sex Transm Inf 1998;74:101-9.
2. Derkay CS, Darrow DH. Recurrent respiratory papillomatosis of the larynx: current diagnosis and treatment. Otolaryngol Clin North Am 2000;33(5):1127-41.
3. Cornelison TL. Human papillomavirus genotype 16 vaccines for cervical cancer prophylaxis and treatment. Curr Opin Oncol 2000;12:466-73.
4. Muñoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348(6):518-27.
5. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. Vaccine 2006;24(Suppl 3):S11-S25.
6. Lacey CJN, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine 2006;24(Supplement 3):S3-35-S3/41.
7. Iskander J. Quadrivalent human papillomavirus vaccine (HPV4): summary of post-licensure safety monitoring, 2008. Presented at the Advisory Committee on Immunization Practices Meeting, Atlanta, October 22, 2008. http://www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-oct08/15-6-hpv.pdf
8. Calugar A. Quadrivalent human papillomavirus vaccine (HPV4): post-licensure safety update, vaccine adverse event reporting system (VAERS), United States, 2008. Presented at the Advisory Committee on Immunization Practices Meeting, Atlanta, October 22, 2008. http://www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-oct08/12-3-hpv.pdf
9. Gee J, Naleway A, Shui I. Vaccine safety datalink project: monitoring the safety of quadrivalent human papillomavirus vaccine (HPV4), 2008. Presented at the Advisory Committee on Immunization Practices Meeting, Atlanta, October 22, 2008. http://www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-oct08/14-5-hpv.pdf
10. Giuliano AR, Lu B, Nielson CM, Flores R, Papenfuss MR, Lee JH, et al. Age-specific prevalence, incidene, and duration of human papillomavirus infections in a chohort of 290 US men. J Infect Dis 2008;198:827-35.
11. Grce M, Husnjak K, Skerlev M, Lipozencic J, Pavelic K. Detection and typing of human papillomaviruses by means of polymerase chain reaction and fragment length polymorphism in male genital lesions. Anticancer Res 2000;20:2097-102.
12. Aubin F, Pretet J-L, Jacquard A-C, Saunier M, Carcopino X, Jaroud F, et al. Human papillomavirus genotype distribution in external acuminata condylomata: a large French national study (EDiTH IV). Clin Inf Dis 2008;47:610-5.

13. Potocnik M, Kocjan BJ, Seme K, Poljak M. Distribution of human papillomavirus (HPV) genotypes in genital warts from males in Slovenia. Acta Dermatoven APA 2007;16(3):91-8.

14. Sakuma S, Minagawa H, Mori R, Kumazawa J, Sagiyama K, Yanagi K. Human papillomavirus DNA in condylomata acuminata from Japanese males. Diagn Microbiol Infect Dis 1988;10:23-9.

15. Hillman RJ, Botcherby M, Ryait BK, Hanna N, Taylor-Robinson D. Detection of human papillomavirus DNA in the urogenital tracts of men with anogenital warts. Sex Transm Dis 1993;20(1):21-7.

16. Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. Clin Infect Dis 2003;36:1397-403.

17. Centers for Disease Control and Prevention. Sexually Transmitted Diseases, Surveillance & Statistics, Surveillance Reports 2007, Table 42: Selected STDs and complications--initial visits to physicians' offices, National Disease and Therapeutic Index: United States, 1966-2007. http://www.cdc.gov/STD/stats07/tables/42.htm

18. Koshiol JE, St.Laurent SA, Pimenta JM. Rate and predictors of new genital warts claims and genital warts-related healthcare utilization among privately insured patients in the United States. Sex Transmit Dis 2004;31(12):748-52.

19. Maw RD, Reitano M, Roy M. An international survey of patients with genital warts: perceptions regarding treatment and impact on lifestyle. International Journl of STD & AIDS 1998;9:571-8.

20. Woodhall S, Ramsey T, Cai C, Crouch S, Jit M, Birks Y, et al. Estimation of the impact of genital warts on health-related quality of life. Sex Transm Inf 2008;84(3):161-6;328.

21. Marra C, Ogilvie G, Gastonguay L, Colley L, Taylor D, Marra F. Patients with genital warts have a decreased quality of life. Sex Transm Dis 2009;36(4):258-60.

22. Maw R. Critical appraisal of commonly used treatment for genital warts. Int J STD AIDS 2004;15:357-64.

23. Kodner CM, Nasraty S. Management of genital warts. Am Fam Physician 2004;70(12):2335-42.

24. Insinga RP, Dasbach EJ, Elbasha EH. Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US: analytic framework and review of the literature. Pharmacoeconomics 2005;23(11):1107-22.

25. Dillner J, von Krogh G, Horenblas S, Meijer CJLM. Etiology of squamous cell carcinoma of the penis. Scan J Urol Nephrol 2000;34(1 supp 205):189-93.

26. Rubin MA, Kleter B, Zhou M, Ayala G, Cubilla AL, Quint WGV, et al. Detection and typing of human papillomavirus DNA in penile carcinoma: Evidence for multiple independent pathways of penile carcinogenesis. Am J Pathol 2001;159(4):1211-8.

27. Giuliano AR, Salmon D. The case for a gender-neutral (universal) human papillomavirus vaccination policy in the United States: point. Cancer Epidemiol Biomarkers Prev 2008;17(4):805-8.

28. World Health Organization. IARC monographs on the evaluation of carcinogenic risks to humans: volume 90, human papillomaviruses, 2007.

29. Misra S, Chaturvedi A, Misra NC. Penile carcinoma: a challenge for the developing World. Lancet Oncol 2004;5:240-7.

30. Ornellas AA, Seixas ALC, Marota A, Wisnescky A, Campos F, de Moraes JR. Surgical treatment of invasive squamous cell carcinoma of the penis: retrospective analysis of 350 cases. J Urol 1994;151:1244-9.

31. Wabinga HR, Parkin DM, Wabwire-Mangen F, Nambooze S. Trends in cancer incidence in Kyadondo County, Uganda, 1960-1997. Br J Cancer 2000;82(9):1585-92.

32. American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society. http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf

33. Rippentrop JM, Joslyn SA, Konety BR. Squamous cell carcinoma of the penis: evaluation of data from the surveillance, epidemiology, and end results program. Cancer 2004;101(6):1357-63.

34. D'ancona CAL, Botega NJ, De Moraes C, Da Silva Lavoura JN, Santos JK, Netto JNR. Quality of life after partial penectomy for penile carcinoma. Urology 1997;50(4):593-6.

35. Ficarra V, Mofferdin A, D'Amico A, Zanon G, Schiavone D, Malossini G, et al. Comparaison de la qualite de vie des patients traites pour cancer epidermoide de la verge par chirurgie ou radiotherapie (Quality of life in patients who have undergone surgical or radiotherapeutic treatment for squamous cancer of the penis). Prog Urol 1999;9:715-20 (translated title).

36. Gross G, Pfister H. Role of human papillomavirus in penile cancer, penile intraepithelial squamous cell neoplasias and in genital warts. Med Microbiol Immunol 2004;193:35-44.

37. Cupp MR, Malek RS, Goellner JR, Smith TF, Espy MJ. The detection of human papillomavirus deoxyribonucleic acid in intraepithelial, in situ, verrucous and invasive carcinoma of the penis. J Urol 1995;154:1024-9.

38. Demeter LM, Stoler MH, Bonnez W, Corey L, Pappas P, Strussenberg J, et al. Penile intraepithelial neoplasia: clinical presentation and an analysis of the physical state of human papillomavirus DNA. J Infect Dis 1993;168:38-46.

39. Mikhail GR. Cancers, precancers, and pseudocancers on the male genitalia. A review of clinical appearances, histopathology, and management. J Dermatol Surg Oncol 1980;6(12):1027-35.

40. Schellhammer PF, Jordan GH, Robey EL, Spaulding JT. Premalignant lesions and nonsquamous malignancy of the penis and carcinoma of the scrotum. Urol Clin North Am 1992;19(1):131-42.

41. Frisch M, Melbye M, Moller H. Trends in incidence of anal cancer in Denmark. Br Med J 1993;306:419-22.

42. Johnson LG, Madeleine MM, Newcomer LM, Schwartz SM, Daling JR. Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. Cancer 2004;101(2):281-8.

43. Melbye M, Rabkin C, Frisch M, Biggar RJ. Changing patterns of anal cancer incidence in the United States. Am J Epidemiol 1994;139(8):772-80.

44. Vatra B, Sobhani I, Aparicio T, Girard P-M, du Puy Montbrun T, Housset M, et al. Caractéristiques cliniques, thérapeutiques et pronostiques des carcinomes épidermoïdes du canal anal chez les malades VIH positifs (Anal canal squamous-cell carcinomas in HIV positive patients: clinical features, treatments, and prognosis). Gastroenterol Clin Biol 2002;26:150-6 (translated abstract).

45. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer 2004;101(2):270-80.

46. Frisch M, Glimelius B, van den Brule AJC, Wohlfahrt J, Meijer CJLM, Walboomers JMM, et al. Sexually transmitted infection as a cause of anal cancer. N Eng J Med 1997;337(19):1350-8.

47. Frisch M, Glimelius B, Wohlfahrt J, Adami H-O, Melbye M. Tobacco smoking as a risk factor in anal carcinoma: an antiestrogenic mechanism? J Natl Cancer Inst 1999;91(8):708-15.

48. Tilston P. Anal human papillomavirus and anal cancer. J Clin Pathol 1997;50:625-34.

49. DeVuyst H, Clifford G, Nascimento MC, Madeleine M, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;124(7):1626-36.

50. Critchlow CW, Surawicz CM, Holmes KK, Kuypers J, Daling JR, Hawes SE, et al. Prospective study of high grade anal squamous intraepithelial neoplasia in a cohort of homosexual men: influence of HIV infection, immunosuppression and human papillomavirus infection. AIDS 1995;9(11):1255-62.

51. Sobhani I, Walker F, Roudot-Thoraval F, Abramowitz L, Johanet H, Hénin D, et al. Anal carcinoma: incidence and effect of cumulative infections. AIDS 2004;18(11):1561-9.

52. Scholefield JH, Ogunbiyi OA, Smith JHF, Rogers K, Sharp F. Treatment of anal intraepithelial neoplasia. Br J Surg 1994;81:1238-40.

53. Palefsky JM, Holly EA, Ralston ML, Jay N, Berry JM, Darragh TM. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. AIDS 1998;12(5):495-503.

54. Scholefield JH, Castle MT, Watson NFS. Malignant transformation of high-grade anal intraepithelial neoplasia. Br J Surg 2005;92:1133-6.

55. Watson AJM, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intra-epithelial neoplasia. ANZ J Surg 2006;76:715-7.

56. Mork J, Lie AK, Glattre E, Hallmans G, Jellum E, Koskela P, et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. N Engl J Med 2001;344(15):1125-31.

57. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Eng J Med 2007;356(19):1944-56.

58. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000;92(9):709-20.

59. Derkay CS, Darrow DH. Recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 2006;115(1):1-11.

60. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am J Epidemiol 2003;157(3):218-26.

61. Ho GYF, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med 1998;338(7):423-8.

62. Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK, et al. Condom use and the risk of genital human papillomavirus infection in young women. N Eng J Med 2006;354(25):2645-54.

63. Barrasso R, De Brux J, Croissant O, Orth G. High prevalence of papillomavirus-associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia. N Engl J Med 1987;317:916-23.

64. Bosch FX, Castellsagué X, Muñoz N, de Sanjosé S, Ghaffari AM, González LC, et al. Male sexual behavior and human papillomavirus DNA: key risk factors for cervical cancer in Spain. J Natl Cancer Inst 1996;88(15):1060-7.

65. Agarwal SS, Sehgal A, Sardana S, Kumar A, Luthra UK. Role of male behavior in cervical carcinogenesis among women with one lifetime sexual partner. Cancer 1993;72(5):1666-969.

66. Thomas DB, Ray RM, Pardthaisong T, Chutivongse S, Koetsawang S, Silpisornosol S, et al. Prostitution, condom use, and invasive squamous cell cervical cancer in Thailand. Am J Epidemiol 1996;143(8):779-86.

67. Thomas DB, Ray RM, Kuypers J, Kiviat N, Koetsawang A, Ashley RL, et al. Human papillomaviruses and cervical cancer in Bangkok III: the role of husbands and commercial sex workers. Am J Epidemiol 2001;153(8):740-8.

68. Buckley JD, Doll R, Harris RWC, Vessey MP, Williams PT. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981;318(8254):1010-4.

69. Winer RL, Feng Q, Hughes JP, O'Reilly S, Kiviat NB, Koutsky LA. Risk of female human papillomavirus acquisition associated with first male sex partner. J Infect Dis 2008;197:279-82.

70. Hernandez BY, Wilkens LR, Zhu X, Thompson P, McDuffie K, Shvetsov YB, et al. Transmission of human papillomavirus in heterosexual couples. Emerg Infect Dis 2008;14(6):888-94.

71. Lea W, Farhat S, Jonte J, Breland D, Ma Y, Godwin de Medina C, et al. Type-specific HPV concordance among monogamous couples in whom the woman had a recently detected, incident HPV type [abstract]. 24th International Papillomavirus Conference and Clinical Workshop; 2007 Nov 3-09. Beijing, China. Beijing International Convention Center: International Papillomavirus Society; Chinese Medical Association, 2007.

72. Weaver BA, Feng Q, Holmes KK, Kiviat N, Lee SK, Meyer C, et al. Evaluation of genital sites and sampling techniques for detection of human papillomavirus DNA in men. J Infect Dis 2004;189:677-85.

73. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75(4):800-2.

74. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.